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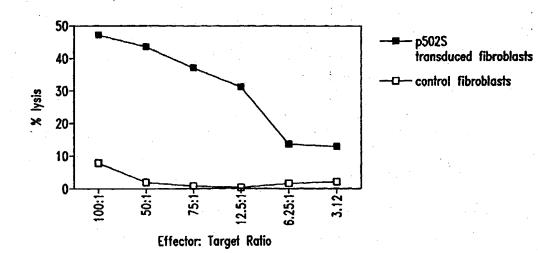
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(54) Title: COMPOSITIONS AND METHODS FOR THERAPY AND DIAGNOSIS OF PROSTATE CANCER



(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, such as prostate cancer, are disclosed. Compositions may comprise one or more prostate tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a prostate tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as prostate cancer. Diagnostic methods based on detecting a prostate tumor protein, or mRNA encoding such a protein, in a sample are also provided.

WO 01/252

# COMPOSITIONS AND METHODS FOR THERAPY AND DIAGNOSIS OF PROSTATE CANCER

#### TECHNICAL FIELD

The present invention relates generally to therapy and diagnosis of cancer, such as prostate cancer. The invention is more specifically related to polypeptides comprising at least a portion of a prostate tumor protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides may be used in vaccines and pharmaceutical compositions for prevention and treatment of prostate cancer, and for the diagnosis and monitoring of such cancers.

#### BACKGROUND OF THE INVENTION

Prostate cancer is the most common form of cancer among males, with an estimated incidence of 30% in men over the age of 50. Overwhelming clinical evidence shows that human prostate cancer has the propensity to metastasize to bone, and the disease appears to progress inevitably from androgen dependent to androgen refractory status, leading to increased patient mortality. This prevalent disease is currently the second leading cause of cancer death among men in the U.S.

In spite of considerable research into therapies for the disease, prostate cancer remains difficult to treat. Commonly, treatment is based on surgery and/or radiation therapy, but these methods are ineffective in a significant percentage of cases. Two previously identified prostate specific proteins - prostate specific antigen (PSA) and prostatic acid phosphatase (PAP) - have limited therapeutic and diagnostic potential. For example, PSA levels do not always correlate well with the presence of prostate cancer, being positive in a percentage of non-prostate cancer cases, including benign prostatic hyperplasia (BPH). Furthermore, PSA measurements correlate with prostate volume, and do not indicate the level of metastasis.

In spite of considerable research into therapies for these and other cancers, prostate cancer remains difficult to diagnose and treat effectively. Accordingly, there is a need in the art for improved methods for detecting and treating

such cancers. The present invention fulfills these needs and further provides other related advantages.

#### SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compositions and methods for the diagnosis and therapy of cancer, such as prostate cancer. In one aspect, the present invention provides polypeptides comprising at least a portion of a prostate tumor protein, or a variant thereof. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises at least an immunogenic portion of a prostate tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of: (a) sequences recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472; (b) sequences that hybridize to any of the foregoing sequences under moderately stringent conditions; and (c) complements of any of the sequence of (a) or (b). In certain specific embodiments, such a polypeptide comprises at least a portion, or variant thereof, of a tumor protein that includes an amino acid sequence selected from the group consisting of sequences recited in any one of SEO ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380 and 383.

The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least 15 amino acid residues of a prostate tumor protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, vaccines are provided. Such vaccines comprise a polypeptide or polynucleotide as described above and a non-specific immune response enhancer.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a prostate tumor protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, vaccines are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a non-specific immune response enhancer.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Vaccines are further provided, within other aspects, that comprise a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a non-specific immune response enhancer.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition or vaccine as recited above.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a prostate tumor protein, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a prostate tumor protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polypucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of a prostate tumor protein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be prostate cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount

detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

#### BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Figure 1 illustrates the ability of T cells to kill fibroblasts expressing the representative prostate tumor polypeptide P502S, as compared to control fibroblasts. The percentage lysis is shown as a series of effector:target ratios, as indicated.

Figures 2A and 2B illustrate the ability of T cells to recognize cells expressing the representative prostate tumor polypeptide P502S. In each case, the number of  $\gamma$ -interferon spots is shown for different numbers of responders. In Figure 2A, data is presented for fibroblasts pulsed with the P2S-12 peptide, as compared to fibroblasts pulsed with a control E75 peptide. In Figure 2B, data is presented for fibroblasts expressing P502S, as compared to fibroblasts expressing HER-2/neu.

Figure 3 represents a peptide competition binding assay showing that the P1S#10 peptide, derived from P501S, binds HLA-A2. Peptide P1S#10 inhibits HLA-A2 restricted presentation of fluM58 peptide to CTL clone D150M58 in TNF release bioassay. D150M58 CTL is specific for the HLA-A2 binding influenza matrix peptide fluM58.

Figure 4 illustrates the ability of T cell lines generated from P1S#10 immunized mice to specifically lyse P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat A2Kb targets, as compared to EGFP-transduced Jurkat A2Kb. The percent lysis is shown as a series of effector to target ratios, as indicated.

Figure 5 illustrates the ability of a T cell clone to recognize and specifically lyse Jurkat A2Kb cells expressing the representative prostate tumor polypeptide P501S, thereby demonstrating that the P1S#10 peptide may be a naturally processed epitope of the P501S polypeptide.

Figures 6A and 6B are graphs illustrating the specificity of a CD8<sup>+</sup> cell line (3A-1) for a representative prostate tumor antigen (P501S). Figure 6A shows the results of a <sup>51</sup>Cr release assay. The percent specific lysis is shown as a series of effector:target ratios, as indicated. Figure 6B shows the production of interferongamma by 3A-1 cells stimulated with autologous B-LCL transduced with P501S, at varying effector:target rations as indicated.

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SEQ ID NO: 2 is the determined 3' cDNA sequence for F1-12

SEQ ID NO: 3 is the determined 5' cDNA sequence for F1-12

SEQ ID NO: 4 is the determined 3' cDNA sequence for F1-16

SEQ ID NO: 5 is the determined 3' cDNA sequence for H1-1

SEQ ID NO: 6 is the determined 3' cDNA sequence for H1-9

SEO ID NO: 7 is the determined 3' cDNA sequence for H1-4

SEQ ID NO: 8 is the determined 3' cDNA sequence for J1-17

SEQ ID NO: 9 is the determined 5' cDNA sequence for J1-17

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SEQ ID NO: 109 is the determined full length cDNA sequence for J1-17

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SEQ ID NO: 199 is the determined extended cDNA sequence for 1H-4772 SEO ID NO: 200 is the determined extended cDNA sequence for 1D-4309 SEQ ID NO: 201 is the determined extended cDNA sequence for 1D.1-4278 SEO ID NO: 202 is the determined extended cDNA sequence for 1D-4288 SEQ ID NO: 203 is the determined extended cDNA sequence for 1D-4283 SEO ID NO: 204 is the determined extended cDNA sequence for 1D-4304 SEQ ID NO: 205 is the determined extended cDNA sequence for 1D-4296 SEQ ID NO: 206 is the determined extended cDNA sequence for 1D-4280 SEQ ID NO: 207 is the determined cDNA sequence for 10-d8fwd SEQ ID NO: 208 is the determined cDNA sequence for 10-H10con SEQ ID NO: 209 is the determined cDNA sequence for 11-C8rev SEQ ID NO: 210 is the determined cDNA sequence for 7.g6fwd SEQ ID NO: 211 is the determined cDNA sequence for 7.g6rev SEQ ID NO: 212 is the determined cDNA sequence for 8-b5fwd SEQ ID NO: 213 is the determined cDNA sequence for 8-b5rev SEQ ID NO: 214 is the determined cDNA sequence for 8-b6fwd SEQ ID NO: 215 is the determined cDNA sequence for 8-b6 rev SEQ ID NO: 216 is the determined cDNA sequence for 8-d4fwd SEQ ID NO: 217 is the determined cDNA sequence for 8-d9rev SEQ ID NO: 218 is the determined cDNA sequence for 8-g3fwd SEQ ID NO: 219 is the determined cDNA sequence for 8-g3rev SEQ ID NO: 220 is the determined cDNA sequence for 8-h11rev SEQ ID NO: 221 is the determined cDNA sequence for g-f12fwd SEQ ID NO: 222 is the determined cDNA sequence for g-f3rev SEQ ID NO: 223 is the determined cDNA sequence for P509S SEQ ID NO: 224 is the determined cDNA sequence for P510S SEQ ID NO: 225 is the determined cDNA sequence for P703DE5 SEQ ID NO: 226 is the determined cDNA sequence for 9-A11 SEQ ID NO: 227 is the determined cDNA sequence for 8-C6 SEQ ID NO: 228 is the determined cDNA sequence for 8-H7

SEQ ID NO: 229 is the determined cDNA sequence for JPTPN13 SEQ ID NO: 230 is the determined cDNA sequence for JPTPN14 SEQ ID NO: 231 is the determined cDNA sequence for JPTPN23 SEQ ID NO: 232 is the determined cDNA sequence for JPTPN24 SEQ ID NO: 233 is the determined cDNA sequence for JPTPN25 SEQ ID NO: 234 is the determined cDNA sequence for JPTPN30 SEQ ID NO: 235 is the determined cDNA sequence for JPTPN34 SEQ ID NO: 236 is the determined cDNA sequence for PTPN35 SEQ ID NO: 237 is the determined cDNA sequence for JPTPN36 SEQ ID NO: 238 is the determined cDNA sequence for JPTPN38 SEQ ID NO: 239 is the determined cDNA sequence for JPTPN39 SEQ ID NO: 240 is the determined cDNA sequence for JPTPN40 SEQ ID NO: 241 is the determined cDNA sequence for JPTPN41 SEQ ID NO: 242 is the determined cDNA sequence for JPTPN42 SEQ ID NO: 243 is the determined cDNA sequence for JPTPN45 SEQ ID NO: 244 is the determined cDNA sequence for JPTPN46 SEQ ID NO: 245 is the determined cDNA sequence for JPTPN51 SEQ ID NO: 246 is the determined cDNA sequence for JPTPN56 SEQ ID NO: 247 is the determined cDNA sequence for PTPN64 SEQ ID NO: 248 is the determined cDNA sequence for JPTPN65 SEQ ID NO: 249 is the determined cDNA sequence for JPTPN67 SEQ ID NO: 250 is the determined cDNA sequence for JPTPN76 SEQ ID NO: 251 is the determined cDNA sequence for JPTPN84 SEQ ID NO: 252 is the determined cDNA sequence for JPTPN85 SEQ ID NO: 253 is the determined cDNA sequence for JPTPN86 SEQ ID NO: 254 is the determined cDNA sequence for JPTPN87 SEQ ID NO: 255 is the determined cDNA sequence for JPTPN88 SEQ ID NO: 256 is the determined cDNA sequence for JP1F1 SEQ ID NO: 257 is the determined cDNA sequence for JP1F2 SEQ ID NO: 258 is the determined cDNA sequence for JP1C2

SEO ID NO: 259 is the determined cDNA sequence for JP1B1 SEO ID NO: 260 is the determined cDNA sequence for JP1B2 SEQ ID NO: 261 is the determined cDNA sequence for JP1D3 SEQ ID NO: 262 is the determined cDNA sequence for JP1A4 SEQ ID NO: 263 is the determined cDNA sequence for JP1F5 SEQ ID NO: 264 is the determined cDNA sequence for JP1E6 SEQ ID NO: 265 is the determined cDNA sequence for JP1D6 SEQ ID NO: 266 is the determined cDNA sequence for JP1B5 SEQ ID NO: 267 is the determined cDNA sequence for JP1A6 SEQ ID NO: 268 is the determined cDNA sequence for JP1E8 SEQ ID NO: 269 is the determined cDNA sequence for JP1D7 SEQ ID NO: 270 is the determined cDNA sequence for JP1D9 SEQ ID NO: 271 is the determined cDNA sequence for JP1C10 SEQ ID NO: 272 is the determined cDNA sequence for JP1A9 SEQ ID NO: 273 is the determined cDNA sequence for JP1F12 SEQ ID NO: 274 is the determined cDNA sequence for JP1E12 SEQ ID NO: 275 is the determined cDNA sequence for JP1D11 SEQ ID NO: 276 is the determined cDNA sequence for JP1C11 SEQ ID NO: 277 is the determined cDNA sequence for JP1C12 SEQ ID NO: 278 is the determined cDNA sequence for JP1B12 SEQ ID NO: 279 is the determined cDNA sequence for JP1A12 SEQ ID NO: 280 is the determined cDNA sequence for JP8G2 SEQ ID NO: 281 is the determined cDNA sequence for JP8H1 SEQ ID NO: 282 is the determined cDNA sequence for JP8H2 SEQ ID NO: 283 is the determined cDNA sequence for JP8A3 SEQ ID NO: 284 is the determined cDNA sequence for JP8A4 SEQ ID NO: 285 is the determined cDNA sequence for JP8C3 SEQ ID NO: 286 is the determined cDNA sequence for JP8G4 SEQ ID NO: 287 is the determined cDNA sequence for JP8B6 SEQ ID NO: 288 is the determined cDNA sequence for JP8D6

SEQ ID NO: 289 is the determined cDNA sequence for JP8F5 SEQ ID NO: 290 is the determined cDNA sequence for JP8A8 SEQ ID NO: 291 is the determined cDNA sequence for JP8C7 SEQ'ID NO: 292 is the determined cDNA sequence for JP8D7 SEQ ID NO: 293 is the determined cDNA sequence for P8D8 SEQ ID NO: 294 is the determined cDNA sequence for JP8E7 SEQ ID NO: 295 is the determined cDNA sequence for JP8F8 SEQ ID NO: 296 is the determined cDNA sequence for JP8G8 SEQ ID NO: 297 is the determined cDNA sequence for JP8B10 SEQ ID NO: 298 is the determined cDNA sequence for JP8C10 SEQ ID NO: 299 is the determined cDNA sequence for JP8E9 SEQ ID NO: 300 is the determined cDNA sequence for JP8E10 SEQ ID NO: 301 is the determined cDNA sequence for JP8F9 SEQ ID NO: 302 is the determined cDNA sequence for JP8H9 SEQ ID NO: 303 is the determined cDNA sequence for JP8C12 SEQ ID NO: 304 is the determined cDNA sequence for JP8E11 SEO ID NO: 305 is the determined cDNA sequence for JP8E12 SEQ ID NO: 306 is the amino acid sequence for the peptide PS2#12 SEQ ID NO: 307 is the determined cDNA sequence for P711P SEQ ID NO: 308 is the determined cDNA sequence for P712P SEQ ID NO: 309 is the determined cDNA sequence for CLONE23 SEQ ID NO: 310 is the determined cDNA sequence for P774P SEQ ID NO: 311 is the determined cDNA sequence for P775P SEQ ID NO: 312 is the determined cDNA sequence for P715P SEQ ID NO: 313 is the determined cDNA sequence for P710P SEQ ID NO: 314 is the determined cDNA sequence for P767P SEQ ID NO: 315 is the determined cDNA sequence for P768P SEQ ID NO: 316-325 are the determined cDNA sequences of previously isolated genes SEQ ID NO: 326 is the determined cDNA sequence for P703PDE5 SEQ ID NO: 327 is the predicted amino acid sequence for P703PDE5

SEQ ID NO: 328 is the determined cDNA sequence for P703P6.26

SEQ ID NO: 329 is the predicted amino acid sequence for P703P6.26

SEQ ID NO: 330 is the determined cDNA sequence for P703PX-23

SEQ ID NO: 331 is the predicted amino acid sequence for P703PX-23

SEQ ID NO: 332 is the determined full length cDNA sequence for P509S

SEQ ID NO: 333 is the determined extended cDNA sequence for P707P (also referred

to as 11-C9)

SEQ ID NO: 334 is the determined cDNA sequence for P714P

SEO ID NO: 335 is the determined cDNA sequence for P705P (also referred to as 9-

F3)

SEQ ID NO: 336 is the predicted amino acid sequence for P705P

SEQ ID NO: 337 is the amino acid sequence of the peptide P1S#10

SEQ ID NO: 338 is the amino acid sequence of the peptide p5

SEO ID NO: 339 is the predicted amino acid sequence of P509S

SEO ID NO: 340 is the determined cDNA sequence for P778P

SEQ ID NO: 341 is the determined cDNA sequence for P786P

SEO ID NO: 342 is the determined cDNA sequence for P789P

SEQ ID NO: 343 is the determined cDNA sequence for a clone showing homology to

Homo sapiens MM46 mRNA

SEO ID NO: 344 is the determined cDNA sequence for a clone showing homology to

Homo sapiens TNF-alpha stimulated ABC protein (ABC50) mRNA

SEQ ID NO: 345 is the determined cDNA sequence for a clone showing homology to

Homo sapiens mRNA for E-cadherin

SEO ID NO: 346 is the determined cDNA sequence for a clone showing homology to

Human nuclear-encoded mitochondrial serine hydroxymethyltransferase (SHMT)

SEO ID NO: 347 is the determined cDNA sequence for a clone showing homology to

Homo sapiens natural resistance-associated macrophage protein2 (NRAMP2)

SEO ID NO: 348 is the determined cDNA sequence for a clone showing homology to

Homo sapiens phosphoglucomutase-related protein (PGMRP)

SEQ ID NO: 349 is the determined cDNA sequence for a clone showing homology to

Human mRNA for proteosome subunit p40

SEQ ID NO: 350 is the determined cDNA sequence for P777P

SEQ ID NO: 351 is the determined cDNA sequence for P779P

SEQ ID NO: 352 is the determined cDNA sequence for P790P

SEQ ID NO: 353 is the determined cDNA sequence for P784P

SEQ ID NO: 354 is the determined cDNA sequence for P776P

SEQ ID NO: 355 is the determined cDNA sequence for P780P

SEQ ID NO: 356 is the determined cDNA sequence for P544S

SEQ ID NO: 357 is the determined cDNA sequence for P745S

SEQ ID NO: 358 is the determined cDNA sequence for P782P

SEQ ID NO: 359 is the determined cDNA sequence for P783P

SEQ ID NO: 360 is the determined cDNA sequence for unknown 17984

SEQ ID NO: 361 is the determined cDNA sequence for P787P

SEQ ID NO: 362 is the determined cDNA sequence for P788P

SEQ ID NO: 363 is the determined cDNA sequence for unknown 17994

SEO ID NO: 364 is the determined cDNA sequence for P781P

SEQ ID NO: 365 is the determined cDNA sequence for P785P

SEQ ID NO: 366-375 are the determined cDNA sequences for splice variants of

B305D.

SEQ ID NO: 376 is the predicted amino acid sequence encoded by the sequence of SEQ

ID NO: 366.

SEO ID NO: 377 is the predicted amino acid sequence encoded by the sequence of SEQ

ID NO: 372.

SEQ ID NO: 378 is the predicted amino acid sequence encoded by the sequence of SEQ

ID NO: 373.

SEQ ID NO: 379 is the predicted amino acid sequence encoded by the sequence of SEQ

ID NO: 374.

SEQ ID NO: 380 is the predicted amino acid sequence encoded by the sequence of SEQ

ID NO: 375.

SEQ ID NO: 381 is the determined cDNA sequence for B716P.

SEQ ID NO: 382 is the determined full-length cDNA sequence for P711P.

SEQ ID NO: 383 is the predicted amino acid sequence for P711P.

SEQ ID NO: 384 is the cDNA sequence for P1000C.

SEQ ID NO: 385 is the cDNA sequence for CGI-82.

SEQ ID NO:386 is the cDNA sequence for 23320.

SEQ ID NO:387 is the cDNA sequence for CGI-69.

SEQ ID NO:388 is the cDNA sequence for L-iditol-2-dehydrogenase.

SEQ ID NO:389 is the cDNA sequence for 23379.

SEQ ID NO:390 is the cDNA sequence for 23381.

SEQ ID NO:391 is the cDNA sequence for KIAA0122.

SEQ ID NO:392 is the cDNA sequence for 23399.

SEQ ID NO:393 is the cDNA sequence for a previously identified gene.

SEQ ID NO:394 is the cDNA sequence for HCLBP.

SEO ID NO:395 is the cDNA sequence for transglutaminase.

SEQ ID NO:396 is the cDNA sequence for a previously identified gene.

SEQ ID NO:397 is the cDNA sequence for PAP.

SEQ ID NO:398 is the cDNA sequence for Ets transcription factor PDEF.

SEQ ID NO:399 is the cDNA sequence for hTGR.

SEQ ID NO:400 is the cDNA sequence for KIAA0295.

SEQ ID NO:401 is the cDNA sequence for 22545.

SEQ ID NO:402 is the cDNA sequence for 22547.

SEO ID NO:403 is the cDNA sequence for 22548.

SEQ ID NO:404 is the cDNA sequence for 22550.

SEQ ID NO:405 is the cDNA sequence for 22551.

SEQ ID NO:406 is the cDNA sequence for 22552.

SEQ ID NO:407 is the cDNA sequence for 22553.

SEQ ID NO:408 is the cDNA sequence for 22558.

SEO ID NO:409 is the cDNA sequence for 22562.

SEQ ID NO:410 is the cDNA sequence for 22565.

SEQ ID NO:411 is the cDNA sequence for 22567. SEQ ID NO:412 is the cDNA sequence for 22568. SEQ ID NO:413 is the cDNA sequence for 22570. SEQ ID NO:414 is the cDNA sequence for 22571. SEQ ID NO:415 is the cDNA sequence for 22572. SEQ ID NO:416 is the cDNA sequence for 22573. SEQ ID NO:417 is the cDNA sequence for 22573. SEQ ID NO:418 is the cDNA sequence for 22575. SEQ ID NO:419 is the cDNA sequence for 22580. SEQ ID NO:420 is the cDNA sequence for 22581. SEO ID NO:421 is the cDNA sequence for 22582. SEQ ID NO:422 is the cDNA sequence for 22583. SEQ ID NO:423 is the cDNA sequence for 22584. SEO ID NO:424 is the cDNA sequence for 22585. SEQ ID NO:425 is the cDNA sequence for 22586. SEQ ID NO:426 is the cDNA sequence for 22587. SEQ ID NO:427 is the cDNA sequence for 22588. SEQ ID NO:428 is the cDNA sequence for 22589. SEQ ID NO:429 is the cDNA sequence for 22590. SEQ ID NO:430 is the cDNA sequence for 22591. SEQ ID NO:431 is the cDNA sequence for 22592. SEQ ID NO:432 is the cDNA sequence for 22593. SEQ ID NO:433 is the cDNA sequence for 22594. SEQ ID NO:434 is the cDNA sequence for 22595. SEO ID NO:435 is the cDNA sequence for 22596. SEQ ID NO:436 is the cDNA sequence for 22847. SEQ ID NO:437 is the cDNA sequence for 22848. SEQ ID NO:438 is the cDNA sequence for 22849. SEQ ID NO:439 is the cDNA sequence for 22851. SEQ ID NO:440 is the cDNA sequence for 22852.

SEQ ID NO:441 is the cDNA sequence for 22853.

SEQ ID NO:442 is the cDNA sequence for 22854.

SEQ ID NO:443 is the cDNA sequence for 22855.

SEQ ID NO:444 is the cDNA sequence for 22856.

SEQ ID NO:445 is the cDNA sequence for 22857.

SEQ ID NO:446 is the cDNA sequence for 23601.

SEQ ID NO:447 is the cDNA sequence for 23602.

SEQ ID NO:448 is the cDNA sequence for 23605.

SEQ ID NO:449 is the cDNA sequence for 23606.

SEQ ID NO:450 is the cDNA sequence for 23612.

SEQ ID NO:451 is the cDNA sequence for 23614.

SEQ ID NO:452 is the cDNA sequence for 23618.

SEQ ID NO:453 is the cDNA sequence for 23622.

SEQ ID NO:454 is the cDNA sequence for folate hydrolase.

SEQ ID NO:455 is the cDNA sequence for LIM protein.

SEQ ID NO:456 is the cDNA sequence for a known gene.

SEQ ID NO:457 is the cDNA sequence for a known gene.

SEQ ID NO:458 is the cDNA sequence for a previously identified gene.

SEQ ID NO:459 is the cDNA sequence for 23045.

SEQ ID NO:460 is the cDNA sequence for 23032.

SEQ ID NO:461 is the cDNA sequence for 23054.

SEQ ID NOs:462-467 are cDNA sequences for known genes.

SEQ ID NOs:468-471 are cDNA sequences for P710P.

SEQ ID NO:472 is a cDNA sequence for P1001C.

SEQ ID NO:473 is the amino acid sequence for PSMA.

SEQ ID NO:474 is the amino acid sequence for PAP.

SEQ ID NO:475 is the amino acid sequence for PSA.

SEQ ID NO:476 is the amino acid sequence for a fusion protein containing PSA, P703P and P501S.

#### DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy and diagnosis of cancer, such as prostate cancer. The compositions described herein may include prostate tumor polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (e.g., T cells). Polypeptides of the present invention generally comprise at least a portion (such as an immunogenic portion) of a prostate tumor protein or a variant thereof. A "prostate tumor protein" is a protein that is expressed in prostate tumor cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in a normal tissue, as determined using a representative assay provided herein. Certain prostate tumor proteins are tumor proteins that react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with prostate cancer. Polynucleotides of the subject invention generally comprise a DNA or RNA sequence that encodes all or a portion of such a polypeptide, or that is complementary to such a Antibodies are generally immune system proteins, or antigen-binding fragments thereof, that are capable of binding to a polypeptide as described above. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B-cells that express a polypeptide as described above. T cells that may be employed within such compositions are generally T cells that are specific for a polypeptide as described above.

The present invention is based on the discovery of human prostate tumor proteins. Sequences of polynucleotides encoding certain tumor proteins, or portions thereof, are provided in SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472. Sequences of polypeptides comprising at least a portion of a tumor protein are provided in SEQ ID NOs:112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380 and 383.

#### PROSTATE TUMOR PROTEIN POLYNUCLEOTIDES

Any polynucleotide that encodes a prostate tumor protein or a portion or other variant thereof as described herein is encompassed by the present invention. Preferred polynucleotides comprise at least 15 consecutive nucleotides, preferably at least 30 consecutive nucleotides and more preferably at least 45 consecutive nucleotides, that encode a portion of a prostate tumor protein. More preferably, a polynucleotide encodes an immunogenic portion of a prostate tumor protein. Polynucleotides complementary to any such sequences are also encompassed by the present invention. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (i.e., an endogenous sequence that encodes a prostate tumor protein or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native prostate tumor protein or a portion thereof.

Two polynucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions,

usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 Methods in Enzymology vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) CABIOS 5:151-153; Myers, E.W. and Muller W. (1988) CABIOS 4:11-17; Robinson, E.D. (1971) Comb. Theor 11:105; Santou, N. Nes, M. (1987) Mol. Biol. Evol. 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) Proc. Natl. Acad., Sci. USA 80:726-730.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are

capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding a native prostate tumor protein (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Polynucleotides may be prepared using any of a variety of techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (i.e., expression that is at least five fold greater in a prostate tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Alternatively, polypeptides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as prostate tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion may be used to isolate a full length gene from a suitable library (e.g., a prostate tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with <sup>32</sup>P) using well known techniques. A bacterial or bacteriophage library is then screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences are then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (see Triglia et al., Nucl. Acids Res. 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., PCR Methods Applic. 1:111-19, 1991) and walking PCR (Parker et al., Nucl. Acids. Other methods employing amplification may also be Res. 19:3055-60, 1991). employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence.

Certain nucleic acid sequences of cDNA molecules encoding at least a portion of a prostate tumor protein are provided in SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472. Isolation of these polynucleotides is described below. Each of these prostate tumor proteins was overexpressed in prostate tumor tissue.

Polynucleotide variants may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis. Modifications in a polynucleotide sequence may

also be introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (see Adelman et al., DNA 2:183, 1983). Alternatively, RNA molecules may be generated by in vitro or in vivo transcription of DNA sequences encoding a prostate tumor protein, or portion thereof, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Certain portions may be used to prepare an encoded polypeptide, as described herein. In addition, or alternatively, a portion may be administered to a patient such that the encoded polypeptide is generated in vivo (e.g., by transfecting antigen-presenting cells, such as dendritic cells, with a cDNA construct encoding a prostate tumor polypeptide, and administering the transfected cells to the patient).

A portion of a sequence complementary to a coding sequence (i.e., an antisense polynucleotide) may also be used as a probe or to modulate gene expression. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells of tissues to facilitate the production of antisense RNA. An antisense polynucleotide may be used, as described herein, to inhibit expression of a tumor protein. Antisense technology can be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (see Gee et al., In Huber and Carr, Molecular and Immunologic Approaches, Futura Publishing Co. (Mt. Kisco, NY; 1994)). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (e.g., promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes.

A portion of a coding sequence, or of a complementary sequence, may also be designed as a probe or primer to detect gene expression. Probes may be labeled with a variety of reporter groups, such as radionuclides and enzymes, and are preferably at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length. Primers, as noted above, are preferably 22-30 nucleotides in length.

Any polynucleotide may be further modified to increase stability in vivo. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Such formulations are particularly useful for therapeutic purposes, as described below. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (e.g., avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

#### PROSTATE TUMOR POLYPEPTIDES

Within the context of the present invention, polypeptides may comprise at least an immunogenic portion of a prostate tumor protein or a variant thereof, as described herein. As noted above, a "prostate tumor protein" is a protein that is expressed by prostate tumor cells. Proteins that are prostate tumor proteins also react detectably within an immunoassay (such as an ELISA) with antisera from a patient with prostate cancer. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of a protein that is recognized (i.e., specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a prostate tumor protein or a variant thereof. Certain preferred immunogenic portions include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal deletion (e.g., 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, Fundamental Immunology, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera

and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (i.e., they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. An immunogenic portion of a native prostate tumor protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (e.g., in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, <sup>125</sup>I-labeled Protein A.

As noted above, a composition may comprise a variant of a native prostate tumor protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native prostate tumor protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigen-specific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (e.g., 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein. Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most

preferably at least about 95% identity (determined as described above) to the identified polypeptides.

Preferably, a variant contains conservative substitutions. "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression

vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be

targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

In certain embodiments, the present invention provides fusion proteins comprising a polypeptide disclosed herein together with at least one of the following known prostate antigens: prostate specific antigen (PSA); prostatic acid phosphatase (PAP); and prostate specific membrane antigen (PSMA). The protein sequences for PSMA, PAP and PSA are provided in SEQ ID NO: 473-475, respectively. In certain embodiments, the fusion proteins of the present invention comprise PSA, PAP and/or PSMA in combination with one or more of the following the inventive antigens: P501S (amino acid sequence provided in SEQ ID NO: 113); P703P (amino acid sequences provided in SEO ID NO: 327, 329, 331); P704P (cDNA sequence provided in SEQ ID NO: 67); P712P (cDNA sequence provided in SEQ ID NO: 308); P775P (cDNA sequence provided in SEQ ID NO: 311); P776P (cDNA sequence provided in SEQ ID NO: 354): P790P (cDNA sequence provided in SEQ ID NO: 352). The amino acid sequence of a fusion protein of PSA, P703P and P501S is provided in SEQ ID NO: 476. In preferred embodiments, the inventive fusion proteins comprise one of the following combinations of antigens: PSA and P703P; PSA and P501S; PAP and P703P; PAP and P501S; PSMA and P703P; PSMA and P501S; PSA, PAP and P703P; PSA, PAP and P501S; PSA, PAP, PSMA and P703P, PSA, PAP, PSMA and P501S. One of skill in the art will appreciate that the order of polypeptides within a fusion protein can be altered without substantially changing the therapeutic, prophylactic or diagnostic properties of the fusion protein.

The fusion proteins described above are more immunogenic and will be effective in a greater number of prostate cancer patients than any of the individual components alone. The use of multiple antigens in the form of a fusion protein also lessens the likelihood of immunologic escape.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide

components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., Gene 40:39-46, 1985; Murphy et al., Proc. Natl. Acad. Sci. USA 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. New Engl. J. Med., 336:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (e.g., the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in E. coli (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-

terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

### BINDING AGENTS

The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to a prostate tumor protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a prostate tumor protein if it reacts at a detectable level (within, for example, an ELISA) with a prostate tumor protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10<sup>3</sup> L/mol. The binding constant may be determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as prostate cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a prostate tumor protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal

indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (e.g., blood, sera, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, Eur. J. Immunol. 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988) and digested

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by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include <sup>90</sup>Y, <sup>123</sup>I, <sup>125</sup>I, <sup>131</sup>I, <sup>186</sup>Re, <sup>188</sup>Re, <sup>211</sup>At, and <sup>212</sup>Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, e.g., U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

### T CELLS

Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for a prostate tumor protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the CEPRATE™ system, available from CellPro Inc., Bothell WA (*see also* U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a prostate tumor polypeptide, polynucleotide encoding a prostate tumor polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, a prostate tumor polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a prostate tumor polypeptide if the T cells kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., Cancer Res. 54:1065-1070, 1994. Alternatively,

detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a prostate tumor polypeptide (100 ng/ml - 100 µg/ml, preferably 200 ng/ml - 25 µg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-γ) is indicative of T cell activation (see Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a prostate tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4<sup>+</sup> and/or CD8<sup>+</sup>. Prostate tumor protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from either a patient or a related, or unrelated, donor and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4<sup>+</sup> or CD8<sup>+</sup> T cells that proliferate in response to a prostate tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a prostate tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a prostate tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of a prostate tumor protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

# PHARMACEUTICAL COMPOSITIONS AND VACCINES

Within certain aspects, polypeptides, polynucleotides, T cells and/or binding agents disclosed herein may be incorporated into pharmaceutical compositions

or immunogenic compositions (*i.e.*, vaccines). Pharmaceutical compositions comprise one or more such compounds and a physiologically acceptable carrier. Vaccines may comprise one or more such compounds and a non-specific immune response enhancer. A non-specific immune response enhancer may be any substance that enhances an immune response to an exogenous antigen. Examples of non-specific immune response enhancers include adjuvants, biodegradable microspheres (*e.g.*, polylactic galactide) and liposomes (into which the compound is incorporated; *see e.g.*, Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and vaccines within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition or vaccine.

A pharmaceutical composition or vaccine may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated in situ. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, Crit. Rev. Therap. Drug Carrier Systems 15:143-198, 1998, and references cited therein. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as Bacillus-Calmette-Guerrin) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., Proc. Natl. Acad. Sci. USA 86:317-321, 1989; Flexner et al., Ann. N.Y. Acad. Sci. 569:86-103, 1989; Flexner

et al., Vaccine 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, Biotechniques 6:616-627, 1988; Rosenfeld et al., Science 252:431-434, 1991; Kolls et al., Proc. Natl. Acad. Sci. USA 91:215-219, 1994; Kass-Eisler et al., Proc. Natl. Acad. Sci. USA 90:11498-11502, 1993; Guzman et al., Circulation 88:2838-2848, 1993; and Guzman et al., Cir. Res. 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., Science 259:1745-1749, 1993 and reviewed by Cohen, Science 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Such compositions may also comprise buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide) and/or preservatives. Alternatively, compositions of the present invention may be

formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of non-specific immune response enhancers may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, Bortadella pertussis or Mycobacterium tuberculosis derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically biodegradable microspheres; polysaccharides; polyphosphazenes; derivatized monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the vaccines provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN-γ, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6, IL-10 and TNF-β) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, Ann. Rev. Immunol. 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt.

MPL adjuvants are available from Ribi ImmunoChem Research Inc. (Hamilton, MT; see US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555. Another preferred adjuvant is a saponin, preferably QS21, which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprises an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210. Any vaccine provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient.

The compositions described herein may be administered as part of a sustained release formulation (i.e., a formulation such as a capsule or sponge that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and vaccines to facilitate production of an antigen-specific

immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects per se and/or to be immunologically compatible with the receiver (i.e., matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, Nature 392:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (see Timmerman and Levy, Ann. Rev. Med. 50:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate in situ, with marked cytoplasmic processes (dendrites) visible in vitro) and based on the lack of differentiation markers of B cells (CD19 and CD20), T cells (CD3), monocytes (CD14) and natural killer cells (CD56), as determined using standard assays. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells in vivo or ex vivo, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (see Zitvogel et al., Nature Med. 4:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into

dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcy receptor, mannose receptor and DEC-205 marker. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80 and CD86).

APCs may generally be transfected with a polynucleotide encoding a prostate tumor protein (or portion or other variant thereof) such that the prostate tumor polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place ex vivo, and a composition or vaccine comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs in vivo. In vivo and ex vivo transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., Immunology and cell Biology 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the prostate tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (e.g., vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (e.g., a carrier molecule). Alternatively, a dendritic cell may be

pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

## **CANCER THERAPY**

In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as prostate cancer. Within such methods, pharmaceutical compositions and vaccines are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and vaccines may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides disclosed herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8+ cytotoxic T lymphocytes and CD4+ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The

polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth in vitro, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition in vivo are well known in the art. Such in vitro culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term in vivo. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al., Immunological Reviews 157:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated ex vivo for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions disclosed herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous,

intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (i.e., untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccinedependent generation of cytolytic effector cells capable of killing the patient's tumor cells in vitro. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (e.g., more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-In general, for pharmaceutical compositions and vaccines vaccinated patients. comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 100 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (e.g., more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a prostate tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

### METHODS FOR DETECTING CANCER

In general, a cancer may be detected in a patient based on the presence of one or more prostate tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine and/or tumor biopsies) obtained from

the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as prostate cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a prostate tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length prostate tumor proteins and portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 µg, and preferably about 100 ng to about 1 µg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay.

This assay may be performed by first contacting an antibody that has been immobilized

on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20<sup>TM</sup> (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (i.e., incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with prostate cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20<sup>TM</sup>. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibodypolypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed

and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as prostate cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., Clinical Epidemiology: A Basic Science for Clinical Medicine, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (i.e., sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (i.e., the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use prostate tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such prostate tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a prostate tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient is incubated with a prostate tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated in vitro for 2-9 days (typically 4 days) at 37°C with prostate tumor polypeptide (e.g., 5 - 25 µg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of prostate tumor polypeptide to serve as a control. For CD4<sup>+</sup> T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8+ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a prostate tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a prostate tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (i.e., hybridizes to) a polynucleotide encoding the prostate tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a prostate tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%,

preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a prostate tumor protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes will hybridize to a polynucleotide encoding a polypeptide disclosed herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375 and 381. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich ed., PCR Technology, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the disclosed compositions may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter

performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple prostate tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

### DIAGNOSTIC KITS

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a prostate tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a prostate tumor protein in a biological sample. Such kits generally comprise

at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a prostate tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a prostate tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

## **EXAMPLES**

# EXAMPLE 1 ISOLATION AND CHARACTERIZATION OF PROSTATE TUMOR POLYPEPTIDES

This Example describes the isolation of certain prostate tumor polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library was constructed from prostate tumor poly A<sup>+</sup> RNA using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD 20897) following the manufacturer's protocol. Specifically, prostate tumor tissues were homogenized with polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A<sup>+</sup> RNA was then purified using a Qiagen oligotex spin column mRNA purification kit (Qiagen, Santa Clarita, CA 91355) according to the manufacturer's protocol. First-strand cDNA was synthesized using the Notl/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with EcoRI/BAXI adaptors (Invitrogen, San Diego, CA) and digested with Notl. Following size fractionation with Chroma Spin-1000 columns (Clontech, Palo Alto, CA), the cDNA was ligated into the EcoRI/Notl site of pCDNA3.1 (Invitrogen) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human pancreas cDNA expression library was prepared from a pool of six tissue specimens (Clontech). The cDNA libraries were characterized by determining the number of independent colonies, the percentage of clones that carried insert, the average insert size and by sequence analysis. The prostate tumor library contained  $1.64 \times 10^7$  independent colonies, with 70% of clones having an insert and the average insert size being 1745 base pairs. The normal pancreas cDNA library contained  $3.3 \times 10^6$  independent colonies, with 69% of clones

having inserts and the average insert size being 1120 base pairs. For both libraries, sequence analysis showed that the majority of clones had a full length cDNA sequence and were synthesized from mRNA, with minimal rRNA and mitochondrial DNA contamination.

cDNA library subtraction was performed using the above prostate tumor and normal pancreas cDNA libraries, as described by Hara *et al.* (*Blood*, *84*:189-199, 1994) with some modifications. Specifically, a prostate tumor-specific subtracted cDNA library was generated as follows. Normal pancreas cDNA library (70 μg) was digested with EcoRI, NotI, and SfuI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 100 μl of H<sub>2</sub>O, heat-denatured and mixed with 100 μl (100 μg) of Photoprobe biotin (Vector Laboratories, Burlingame, CA). As recommended by the manufacturer, the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional Photoprobe biotin (50 μl) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23 μl H<sub>2</sub>O to form the driver DNA.

To form the tracer DNA, 10 μg prostate tumor cDNA library was digested with BamHI and XhoI, phenol chloroform extracted and passed through Chroma spin-400 columns (Clontech). Following ethanol precipitation, the tracer DNA was dissolved in 5 μl H<sub>2</sub>O. Tracer DNA was mixed with 15 μl driver DNA and 20 μl of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 °C water bath and incubated for 20 hours (long hybridization [LH]). The reaction mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12 μl H<sub>2</sub>O, mixed with 8 μl driver DNA and 20 μl of 2 x hybridization buffer, and subjected to a hybridization at 68 °C for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into BamHI/XhoI site of chloramphenicol resistant pBCSK\* (Stratagene, La Jolla, CA 92037) and transformed into ElectroMax E.

coli DH10B cells by electroporation to generate a prostate tumor specific subtracted cDNA library (referred to as "prostate subtraction 1").

To analyze the subtracted cDNA library, plasmid DNA was prepared from 100 independent clones, randomly picked from the subtracted prostate tumor specific library and grouped based on insert size. Representative cDNA clones were further characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A (Foster City, CA). Six cDNA clones, hereinafter referred to as F1-13, F1-12, F1-16, H1-1, H1-9 and H1-4, were shown to be abundant in the subtracted prostate-specific cDNA library. The determined 3' and 5' cDNA sequences for F1-12 are provided in SEQ ID NO: 2 and 3, respectively, with determined 3' cDNA sequences for F1-13, F1-16, H1-1, H1-9 and H1-4 being provided in SEQ ID NO: 1 and 4-7, respectively.

The cDNA sequences for the isolated clones were compared to known sequences in the gene bank using the EMBL and GenBank databases (release 96). Four of the prostate tumor cDNA clones, F1-13, F1-16, H1-1, and H1-4, were determined to encode the following previously identified proteins: prostate specific antigen (PSA), human glandular kallikrein, human tumor expression enhanced gene, and mitochondria cytochrome C oxidase subunit II. H1-9 was found to be identical to a previously identified human autonomously replicating sequence. No significant homologies to the cDNA sequence for F1-12 were found.

Subsequent studies led to the isolation of a full-length cDNA sequence for F1-12. This sequence is provided in SEQ ID NO: 107, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 108.

To clone less abundant prostate tumor specific genes, cDNA library subtraction was performed by subtracting the prostate tumor cDNA library described above with the normal pancreas cDNA library and with the three most abundant genes in the previously subtracted prostate tumor specific cDNA library: human glandular kallikrein, prostate specific antigen (PSA), and mitochondria cytochrome C oxidase subunit II. Specifically, 1 µg each of human glandular kallikrein, PSA and mitochondria cytochrome C oxidase subunit II cDNAs in pCDNA3.1 were added to the

driver DNA and subtraction was performed as described above to provide a second subtracted cDNA library hereinafter referred to as the "subtracted prostate tumor specific cDNA library with spike".

Twenty-two cDNA clones were isolated from the subtracted prostate tumor specific cDNA library with spike. The determined 3' and 5' cDNA sequences for the clones referred to as J1-17, L1-12, N1-1862, J1-13, J1-19, J1-25, J1-24, K1-58, K1-63, L1-4 and L1-14 are provided in SEQ ID NOS: 8-9, 10-11, 12-13, 14-15, 16-17, 18-19, 20-21, 22-23, 24-25, 26-27 and 28-29, respectively. The determined 3' cDNA sequences for the clones referred to as J1-12, J1-16, J1-21, K1-48, K1-55, L1-2, L1-6, N1-1858, N1-1860, N1-1861, N1-1864 are provided in SEO ID NOS: 30-40, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to three of the five most abundant DNA species, (J1-17, L1-12 and N1-1862; SEQ ID NOS: 8-9, 10-11 and 12-13, respectively). Of the remaining two most abundant species, one (J1-12; SEQ ID NO:30) was found to be identical to the previously identified human pulmonary surfactant-associated protein, and the other (K1-48; SEQ ID NO:33) was determined to have some homology to R. norvegicus mRNA for 2-arylpropionyl-CoA epimerase. Of the 17 less abundant cDNA clones isolated from the subtracted prostate tumor specific cDNA library with spike, four (J1-16, K1-55, L1-6 and N1-1864; SEQ ID NOS:31, 34, 36 and 40, respectively) were found to be identical to previously identified sequences, two (J1-21 and N1-1860; SEQ ID NOS: 32 and 38, respectively) were found to show some homology to nonhuman sequences, and two (L1-2 and N1-1861; SEQ ID NOS: 35 and 39, respectively) were found to show some homology to known human sequences. No significant homologies were found to the polypeptides J1-13, J1-19, J1-24, J1-25, K1-58, K1-63, L1-4, L1-14 (SEQ ID NOS: 14-15, 16-17, 20-21, 18-19, 22-23, 24-25, 26-27, 28-29, respectively).

Subsequent studies led to the isolation of full length cDNA sequences for J1-17, L1-12 and N1-1862 (SEQ ID NOS: 109-111, respectively). The corresponding predicted amino acid sequences are provided in SEQ ID NOS: 112-114. L1-12 is also referred to as P501S.

In a further experiment, four additional clones were identified by subtracting a prostate tumor cDNA library with normal prostate cDNA prepared from a pool of three normal prostate poly A+ RNA (referred to as "prostate subtraction 2"). The determined cDNA sequences for these clones, hereinafter referred to as U1-3064, U1-3065, V1-3692 and 1A-3905, are provided in SEQ ID NO: 69-72, respectively. Comparison of the determined sequences with those in the gene bank revealed no significant homologies to U1-3065.

A second subtraction with spike (referred to as "prostate subtraction spike 2") was performed by subtracting a prostate tumor specific cDNA library with spike with normal pancreas cDNA library and further spiked with PSA, J1-17, pulmonary surfactant-associated protein, mitochondrial DNA, cytochrome c oxidase subunit II, N1-1862, autonomously replicating sequence, L1-12 and tumor expression enhanced gene. Four additional clones, hereinafter referred to as V1-3686, R1-2330, 1B-3976 and V1-3679, were isolated. The determined cDNA sequences for these clones are provided in SEQ ID NO:73-76, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to V1-3686 and R1-2330.

Further analysis of the three prostate subtractions described above (prostate subtraction 2, subtracted prostate tumor specific cDNA library with spike, and prostate subtraction spike 2) resulted in the identification of sixteen additional clones, referred to as 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1G-4734, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4810, 1I-4811, 1J-4876, 1K-4884 and 1K-4896. The determined cDNA sequences for these clones are provided in SEQ ID NOS: 77-92, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to 1G-4741, 1G-4734, 1I-4807, 1J-4876 and 1K-4896 (SEQ ID NOS: 79, 81, 87, 90 and 92, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4807, 1J-4876, 1K-4884 and 1K-4896, provided in SEQ ID NOS: 179-188 and 191-193,

respectively, and to the determination of additional partial cDNA sequences for 1I-4810 and 1I-4811, provided in SEQ ID NOS: 189 and 190, respectively.

Additional studies with prostate subtraction spike 2 resulted in the isolation of three more clones. Their sequences were determined as described above and compared to the most recent GenBank. All three clones were found to have homology to known genes, which are Cysteine-rich protein, KIAA0242, and KIAA0280 (SEQ ID NO: 317, 319, and 320, respectively). Further analysis of these clones by Synteni microarray (Synteni, Palo Alto, CA) demonstrated that all three clones were over-expressed in most prostate tumors and prostate BPH, as well as in the majority of normal prostate tissues tested, but low expression in all other normal tissues.

An additional subtraction was performed by subtracting a normal prostate cDNA library with normal pancreas cDNA (referred to as "prostate subtraction 3"). This led to the identification of six additional clones referred to as 1G-4761, 1G-4762, 1H-4766, 1H-4770, 1H-4771 and 1H-4772 (SEQ ID NOS: 93-98). Comparison of these sequences with those in the gene bank revealed no significant homologies to 1G-4761 and 1H-4771 (SEQ ID NOS: 93 and 97, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4761, 1G-4762, 1H-4766 and 1H-4772 provided in SEQ ID NOS: 194-196 and 199, respectively, and to the determination of additional partial cDNA sequences for 1H-4770 and 1H-4771, provided in SEQ ID NOS: 197 and 198, respectively.

Subtraction of a prostate tumor cDNA library, prepared from a pool of polyA+ RNA from three prostate cancer patients, with a normal pancreas cDNA library (prostate subtraction 4) led to the identification of eight clones, referred to as 1D-4297, 1D-4309, 1D.1-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280 (SEQ ID NOS: 99-107). These sequences were compared to those in the gene bank as described above. No significant homologies were found to 1D-4283 and 1D-4304 (SEQ ID NOS: 103 and 104, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1D-4309, 1D.1-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280, provided in SEQ ID NOS: 200-206, respectively.

cDNA clones isolated in prostate subtraction 1 and prostate subtraction 2, described above, were colony PCR amplified and their mRNA expression levels in prostate tumor, normal prostate and in various other normal tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity. Two clones (referred to as P509S and P510S) were found to be overexpressed in prostate tumor and normal prostate and expressed at low levels in all other normal tissues tested (liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon). The determined cDNA sequences for P509S and P510S are provided in SEQ ID NO: 223 and 224, respectively. Comparison of these sequences with those in the gene bank as described above, revealed some homology to previously identified ESTs.

Additional, studies led to the isolation of the full-length cDNA sequence for P509S. This sequence is provided in SEQ ID NO: 332, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 339.

# EXAMPLE 2 DETERMINATION OF TISSUE SPECIFICITY OF PROSTATE TUMOR POLYPEPTIDES

Using gene specific primers, mRNA expression levels for the representative prostate tumor polypeptides F1-16, H1-1, J1-17 (also referred to as P502S), L1-12 (also referred to as P501S), F1-12 (also referred to as P504S) and N1-1862 (also referred to as P503S) were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent as described above. First strand synthesis was carried out using 1-2 μg of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 °C for one hour. The cDNA was then amplified by PCR with genespecific primers. To ensure the semi-quantitative nature of the RT-PCR, β-actin was used as an internal control for each of the tissues examined. First, serial dilutions of the first strand cDNAs were prepared and RT-PCR assays were performed using β-actin specific primers. A dilution was then chosen that enabled the linear range amplification of the β-actin template and which was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the β-actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in four different types of tumor tissue (prostate tumor from 2 patients, breast tumor from 3 patients, colon tumor, lung tumor), and sixteen different normal tissues, including prostate, colon, kidney, liver, lung, ovary, pancreas, skeletal muscle, skin, stomach, testes, bone marrow and brain. F1-16 was found to be expressed at high levels in prostate tumor tissue, colon tumor and normal prostate, and at lower levels in normal liver, skin and testes, with expression being undetectable in the other tissues examined. H1-1 was found to be expressed at high levels in prostate tumor, lung tumor, breast tumor, normal prostate, normal colon and normal brain, at much lower levels in normal lung, pancreas, skeletal muscle, skin, small intestine, bone marrow, and was not detected in the other tissues tested. J1-17 (P502S) and L1-12 (P501S) appear to be specifically over-expressed in prostate, with both genes being expressed at high levels in prostate tumor and normal prostate but at low to undetectable levels in all the other tissues examined. N1-1862 (P503S) was found to be over-expressed in 60% of prostate tumors and detectable in normal colon and kidney. The RT-PCR results thus indicate that F1-16, H1-1, J1-17 (P502S), N1-1862 (P503S) and L1-12 (P501S) are either prostate specific or are expressed at significantly elevated levels in prostate.

Further RT-PCR studies showed that F1-12 (P504S) is over-expressed in 60% of prostate tumors, detectable in normal kidney but not detectable in all other tissues tested. Similarly, R1-2330 was shown to be over-expressed in 40% of prostate tumors, detectable in normal kidney and liver, but not detectable in all other tissues tested. U1-3064 was found to be over-expressed in 60% of prostate tumors, and also expressed in breast and colon tumors, but was not detectable in normal tissues.

RT-PCR characterization of R1-2330, U1-3064 and 1D-4279 showed that these three antigens are over-expressed in prostate and/or prostate tumors.

Northern analysis with four prostate tumors, two normal prostate samples, two BPH prostates, and normal colon, kidney, liver, lung, pancrease, skeletal muscle, brain, stomach, testes, small intestine and bone marrow, showed that L1-12 (P501S) is over-expressed in prostate tumors and normal prostate, while being undetectable in other normal tissues tested. J1-17 (P502S) was detected in two prostate tumors and not in the other tissues tested. N1-1862 (P503S) was found to be over-expressed in three prostate tumors and to be expressed in normal prostate, colon and kidney, but not in other tissues tested. F1-12 (P504S) was found to be highly expressed in two prostate tumors and to be undetectable in all other tissues tested.

The microarray technology described above was used to determine the expression levels of representative antigens described herein in prostate tumor, breast tumor and the following normal tissues: prostate, liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon. L1-12 (P501S) was found to be over-expressed in normal prostate and prostate tumor, with some expression being detected in normal skeletal muscle. Both J1-12 and F1-12 (P504S) were found to be over-expressed in prostate tumor, with expression being lower or undetectable in all other tissues tested. N1-1862 (P503S) was found to be expressed at high levels in prostate tumor and normal prostate, and at low levels in normal large intestine and normal colon, with expression being undetectable in all other tissues tested. R1-2330 was found to be over-expressed in prostate tumor and normal prostate, and to be expressed at lower levels in all other tissues tested. 1D-4279 was found to be over-expressed at lower levels in all other tissues tested.

expressed in prostate tumor and normal prostate, expressed at lower levels in normal spinal cord, and to be undetectable in all other tissues tested.

Further microarray analysis to specifically address the extent to which P501S (SEQ ID NO: 110) was expressed in breast tumor revealed moderate over-expression not only in breast tumor, but also in metastatic breast tumor (2/31), with negligible to low expression in normal tissues. This data suggests that P501S may be over-expressed in various breast tumors as well as in prostate tumors.

The expression levels of 32 ESTs (expressed sequence tags) described by Vasmatzis et al. (Proc. Natl. Acad. Sci. USA 95:300-304, 1998) in a variety of tumor and normal tissues were examined by microarray technology as described above. Two of these clones (referred to as P1000C and P1001C) were found to be over-expressed in prostate tumor and normal prostate, and expressed at low to undetectable levels in all other tissues tested (normal aorta, thymus, resting and activated PBMC, epithelial cells, spinal cord, adrenal gland, fetal tissues, skin, salivary gland, large intestine, bone marrow, liver, lung, dendritic cells, stomach, lymph nodes, brain, heart, small intestine, skeletal muscle, colon and kidney. The determined cDNA sequences for P1000C and P1001C are provided in SEQ ID NO: 384 and 472, respectively. The sequence of P1001C was found to show some homology to the previously isolated Human mRNA for JM27 protein. No significant homologies were found to the sequence of P1000C.

The expression of the polypeptide encoded by the full length cDNA sequence for F1-12 (also referred to as P504S; SEQ ID NO: 108) was investigated by immunohistochemical analysis. Rabbit-anti-P504S polyclonal antibodies were generated against the full length P504S protein by standard techniques. Subsequent isolation and characterization of the polyclonal antibodies were also performed by techniques well known in the art. Immunohistochemical analysis showed that the P504S polypeptide was expressed in 100% of prostate carcinoma samples tested (n=5).

The rabbit-anti-P504S polyclonal antibody did not appear to label benign prostate cells with the same cytoplasmic granular staining, but rather with light nuclear staining. Analysis of normal tissues revealed that the encoded polypeptide was found to be expressed in some, but not all normal human tissues. Positive

cytoplasmic staining with rabbit-anti-P504S polyclonal antibody was found in normal human kidney, liver, brain, colon and lung-associated macrophages, whereas heart and bone marrow were negative.

This data indicates that the P504S polypeptide is present in prostate cancer tissues, and that there are qualitative and quantitative differences in the staining between benign prostatic hyperplasia tissues and prostate cancer tissues, suggesting that this polypeptide may be detected selectively in prostate tumors and therefore be useful in the diagnosis of prostate cancer.

### **EXAMPLE 3**

# ISOLATION AND CHARACTERIZATION OF PROSTATE TUMOR POLYPEPTIDES BY PCR-BASED SUBTRACTION

A cDNA subtraction library, containing cDNA from normal prostate subtracted with ten other normal tissue cDNAs (brain, heart, kidney, liver, lung, ovary, placenta, skeletal muscle, spleen and thymus) and then submitted to a first round of PCR amplification, was purchased from Clontech. This library was subjected to a second round of PCR amplification, following the manufacturer's protocol. The resulting cDNA fragments were subcloned into the vector pT7 Blue T-vector (Novagen, Madison, WI) and transformed into XL-1 Blue MRF' E. coli (Stratagene). DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A.

Fifty-nine positive clones were sequenced. Comparison of the DNA sequences of these clones with those in the gene bank, as described above, revealed no significant homologies to 25 of these clones, hereinafter referred to as P5, P8, P9, P18, P20, P30, P34, P36, P38, P39, P42, P49, P50, P53, P55, P60, P64, P65, P73, P75, P76, P79 and P84. The determined cDNA sequences for these clones are provided in SEQ ID NO: 41-45, 47-52 and 54-65, respectively. P29, P47, P68, P80 and P82 (SEQ ID NO: 46, 53 and 66-68, respectively) were found to show some degree of homology to

previously identified DNA sequences. To the best of the inventors' knowledge, none of these sequences have been previously shown to be present in prostate.

Further studies using the PCR-based methodology described above resulted in the isolation of more than 180 additional clones, of which 23 clones were found to show no significant homologies to known sequences. The determined cDNA sequences for these clones are provided in SEQ ID NO: 115-123, 127, 131, 137, 145, 147-151, 153, 156-158 and 160. Twenty-three clones (SEQ ID NO: 124-126, 128-130, 132-136, 138-144, 146, 152, 154, 155 and 159) were found to show some homology to previously identified ESTs. An additional ten clones (SEQ ID NO: 161-170) were found to have some degree of homology to known genes. Larger cDNA clones containing the P20 sequence represent splice variants of a gene referred to as P703P. The determined DNA sequence for the variants referred to as DE1, DE13 and DE14 are provided in SEQ ID NOS: 171, 175 and 177, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 172, 176 and 178, respectively. The determined cDNA sequence for an extended spliced form of P703 is provided in SEQ ID NO: 225. The DNA sequences for the splice variants referred to as DE2 and DE6 are provided in SEQ ID NOS: 173 and 174, respectively.

mRNA Expression levels for representative clones in tumor tissues (prostate (n=5), breast (n=2), colon and lung) normal tissues (prostate (n=5), colon, kidney, liver, lung (n=2), ovary (n=2), skeletal muscle, skin, stomach, small intestine and brain), and activated and non-activated PBMC was determined by RT-PCR as described above. Expression was examined in one sample of each tissue type unless otherwise indicated.

P9 was found to be highly expressed in normal prostate and prostate tumor compared to all normal tissues tested except for normal colon which showed comparable expression. P20, a portion of the P703P gene, was found to be highly expressed in normal prostate and prostate tumor, compared to all twelve normal tissues tested. A modest increase in expression of P20 in breast tumor (n=2), colon tumor and lung tumor was seen compared to all normal tissues except lung (1 of 2). Increased expression of P18 was found in normal prostate, prostate tumor and breast tumor

compared to other normal tissues except lung and stomach. A modest increase in expression of P5 was observed in normal prostate compared to most other normal tissues. However, some elevated expression was seen in normal lung and PBMC. Elevated expression of P5 was also observed in prostate tumors (2 of 5), breast tumor and one lung tumor sample. For P30, similar expression levels were seen in normal prostate and prostate tumor, compared to six of twelve other normal tissues tested. Increased expression was seen in breast tumors, one lung tumor sample and one colon tumor sample, and also in normal PBMC. P29 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to the majority of normal tissues. However, substantial expression of P29 was observed in normal colon and normal lung (2 of 2). P80 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to all other normal tissues tested, with increased expression also being seen in colon tumor.

Further studies resulted in the isolation of twelve additional clones, hereinafter referred to as 10-d8, 10-h10, 11-c8, 7-g6, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3, 8-h11, 9-f12 and 9-f3. The determined DNA sequences for 10-d8, 10-h10, 11-c8, 8-d4, 8-d9, 8-h11, 9-f12 and 9-f3 are provided in SEQ ID NO: 207, 208, 209, 216, 217, 220, 221 and 222, respectively. The determined forward and reverse DNA sequences for 7-g6, 8-b5, 8-b6 and 8-g3 are provided in SEQ ID NO: 210 and 211; 212 and 213; 214 and 215; and 218 and 219, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to the sequence of 9-f3. The clones 10-d8, 11-c8 and 8-h11 were found to show some homology to previously isolated ESTs, while 10-h10, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3 and 9-f12 were found to show some homology to previously identified genes. Further characterization of 7-G6 and 8-G3 showed identity to the known genes PAP and PSA, respectively.

mRNA expression levels for these clones were determined using the micro-array technology described above. The clones 7-G6, 8-G3, 8-B5, 8-B6, 8-D4, 8-D9, 9-F3, 9-F12, 9-H3, 10-A2, 10-A4, 11-C9 and 11-F2 were found to be over-expressed in prostate tumor and normal prostate, with expression in other tissues tested being low or undetectable. Increased expression of 8-F11 was seen in prostate tumor

and normal prostate, bladder, skeletal muscle and colon. Increased expression of 10-H10 was seen in prostate tumor and normal prostate, bladder, lung, colon, brain and large intestine. Increased expression of 9-B1 was seen in prostate tumor, breast tumor, and normal prostate, salivary gland, large intestine and skin, with increased expression of 11-C8 being seen in prostate tumor, and normal prostate and large intestine.

An additional cDNA fragment derived from the PCR-based normal prostate subtraction, described above, was found to be prostate specific by both microarray technology and RT-PCR. The determined cDNA sequence of this clone (referred to as 9-A11) is provided in SEQ ID NO: 226. Comparison of this sequence with those in the public databases revealed 99% identity to the known gene HOXB13.

Further studies led to the isolation of the clones 8-C6 and 8-H7. The determined cDNA sequences for these clones are provided in SEQ ID NO: 227 and 228, respectively. These sequences were found to show some homology to previously isolated ESTs.

PCR and hybridization-based methodologies were employed to obtain longer cDNA sequences for clone P20 (also referred to as P703P), yielding three additional cDNA fragments that progressively extend the 5' end of the gene. These fragments, referred to as P703PDE5, P703P6.26, and P703PX-23 (SEQ ID NO: 326, 328 and 330, with the predicted corresponding amino acid sequences being provided in SEO ID NO: 327, 329 and 331, respectively) contain additional 5' sequence. P703PDE5 was recovered by screening of a cDNA library (#141-26) with a portion of P703P as a probe. P703P6.26 was recovered from a mixture of three prostate tumor cDNAs and P703PX 23 was recovered from cDNA library (#438-48). Together, the additional sequences include all of the putative mature serine protease along with part of the putative signal sequence. Further studies using a PCR-based subtraction library of a prostate tumor pool subtracted against a pool of normal tissues (referred to as JP: PCR subtraction) resulted in the isolation of thirteen additional clones, seven of which did not share any significant homology to known GenBank sequences. The determined cDNA sequences for these seven clones (P711P, P712P, novel 23, P774P, P775P, P710P and P768P) are provided in SEQ ID NO: 307-311, 313 and 315, respectively.

The remaining six clones (SEQ ID NO: 316 and 321-325) were shown to share some homology to known genes. By microarray analysis, all thirteen clones showed three or more fold over-expression in prostate tissues, including prostate tumors, BPH and normal prostate as compared to normal non-prostate tissues. Clones P711P, P712P, novel 23 and P768P showed over-expression in most prostate tumors and BPH tissues tested (n=29), and in the majority of normal prostate tissues (n=4), but background to low expression levels in all normal tissues. Clones P774P, P775P and P710P showed comparatively lower expression and expression in fewer prostate tumors and BPH samples, with negative to low expression in normal prostate.

The full-length cDNA for P711P was obtained by employing the partial sequence of SEQ ID NO: 307 to screen a prostate cDNA library. Specifically, a directionally cloned prostate cDNA library was prepared using standard techniques. One million colonies of this library were plated onto LB/Amp plates. Nylon membrane filters were used to lift these colonies, and the cDNAs which were picked up by these filters were denatured and cross-linked to the filters by UV light. The P711P cDNA fragment of SEQ ID NO: 307 was radio-labeled and used to hybridize with these filters. Positive clones were selected, and cDNAs were prepared and sequenced using an automatic Perkin Elmer/Applied Biosystems sequencer. The determined full-length sequence of P711P is provided in SEQ ID NO: 382, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 383.

Using PCR and hybridization-based methodologies, additional cDNA sequence information was derived for two clones described above, 11-C9 and 9-F3, herein after referred to as P707P and P714P, respectively (SEQ ID NO: 333 and 334). After comparison with the most recent GenBank, P707P was found to be a splice variant of the known gene HoxB13. In contrast, no significant homologies to P714P were found.

Clones 8-B3, P89, P98, P130 and P201 (as disclosed in U.S. Patent Application No. 09/020,956, filed February 9, 1998) were found to be contained within one contiguous sequence, referred to as P705P (SEQ ID NO: 335, with the predicted

amino acid sequence provided in SEQ ID NO: 336), which was determined to be a splice variant of the known gene NKX 3.1.

## EXAMPLE 4 SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

#### **EXAMPLE 5**

## FURTHER ISOLATION AND CHARACTERIZATION OF PROSTATE TUMOR POLYPEPTIDES BY PCR-BASED SUBTRACTION

A cDNA library generated from prostate primary tumor mRNA as described above was subtracted with cDNA from normal prostate. The subtraction was performed using a PCR-based protocol (Clontech), which was modified to generate larger fragments. Within this protocol, tester and driver double stranded cDNA were

separately digested with five restriction enzymes that recognize six-nucleotide restriction sites (MluI, MscI, PvuII, Sall and StuI). This digestion resulted in an average cDNA size of 600 bp, rather than the average size of 300 bp that results from digestion with Rsal according to the Clontech protocol. This modification did not affect the subtraction efficiency. Two tester populations were then created with different adapters, and the driver library remained without adapters.

The tester and driver libraries were then hybridized using excess driver cDNA. In the first hybridization step, driver was separately hybridized with each of the two tester cDNA populations. This resulted in populations of (a) unhybridized tester cDNAs, (b) tester cDNAs hybridized to other tester cDNAs, (c) tester cDNAs hybridized to driver cDNAs and (d) unhybridized driver cDNAs. The two separate hybridization reactions were then combined, and rehybridized in the presence of additional denatured driver cDNA. Following this second hybridization, in addition to populations (a) through (d), a fifth population (e) was generated in which tester cDNA with one adapter hybridized to tester cDNA with the second adapter. Accordingly, the second hybridization step resulted in enrichment of differentially expressed sequences which could be used as templates for PCR amplification with adaptor-specific primers.

The ends were then filled in, and PCR amplification was performed using adaptor-specific primers. Only population (e), which contained tester cDNA that did not hybridize to driver cDNA, was amplified exponentially. A second PCR amplification step was then performed, to reduce background and further enrich differentially expressed sequences.

This PCR-based subtraction technique normalizes differentially expressed cDNAs so that rare transcripts that are overexpressed in prostate tumor tissue may be recoverable. Such transcripts would be difficult to recover by traditional subtraction methods.

In addition to genes known to be overexpressed in prostate tumor, seventy-seven further clones were identified. Sequences of these partial cDNAs are provided in SEQ ID NO: 29 to 305. Most of these clones had no significant homology to database sequences. Exceptions were JPTPN23 (SEQ ID NO: 231; similarity to pig

valosin-containing protein), JPTPN30 (SEQ ID NO: 234; similarity to rat mRNA for proteasome subunit), JPTPN45 (SEQ ID NO: 243; similarity to rat norvegicus cytosolic NADP-dependent isocitrate dehydrogenase), JPTPN46 (SEQ ID NO: 244; similarity to human subclone H8 4 d4 DNA sequence), JP1D6 (SEQ ID NO: 265; similarity to G. gallus dynein light chain-A), JP8D6 (SEQ ID NO: 288; similarity to human BAC clone RG016J04), JP8F5 (SEQ ID NO: 289; similarity to human subclone H8 3 b5 DNA sequence), and JP8E9 (SEQ ID NO: 299; similarity to human Alu sequence).

Additional studies using the PCR-based subtraction library consisting of a prostate tumor pool subtracted against a normal prostate pool (referred to as PT-PN PCR subtraction) yielded three additional clones. Comparison of the cDNA sequences of these clones with the most recent release of GenBank revealed no significant homologies to the two clones referred to as P715P and P767P (SEQ ID NO: 312 and 314). The remaining clone was found to show some homology to the known gene KIAA0056 (SEQ ID NO: 318). Using microarray analysis to measure mRNA expression levels in various tissues, all three clones were found to be over-expressed in prostate tumors and BPH tissues. Specifically, clone P715P was over-expressed in most prostate tumors and BPH tissues by a factor of three or greater, with elevated expression seen in the majority of normal prostate samples and in fetal tissue, but negative to low expression in all other normal tissues. Clone P767P was over-expressed in several prostate tumors and BPH tissues, with moderate expression levels in half of the normal prostate samples, and background to low expression in all other normal tissues tested.

Further analysis, by microarray as described above, of the PT-PN PCR subtraction library and of a DNA subtraction library containing cDNA from prostate tumor subtracted with a pool of normal tissue cDNAs, led to the isolation of 27 additional clones (SEQ ID NO: 340-365 and 381) which were determined to be over-expressed in prostate tumor. The clones of SEQ ID NO: 341, 342, 345, 347, 348, 349, 351, 355-359, 361, 362 and 364 were also found to be expressed in normal prostate. Expression of all 26 clones in a variety of normal tissues was found to be low or undetectable, with the exception of P544S (SEQ ID NO: 356) which was found to be

expressed in small intestine. Of the 26 clones, 10 (SEQ ID NO: 340-349) were found to show some homology to previously identified sequences. No significant homologies were found to the clones of SEQ ID NO: 350-365.

#### **EXAMPLE 6**

### PEPTIDE PRIMING OF MICE AND PROPAGATION OF CTL LINES

6.1. This Example illustrates the preparation of a CTL cell line specific for cells expressing the P502S gene.

Mice expressing the transgene for human HLA A2.1 (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with P2S#12 peptide (VLGWVAEL; SEQ ID NO: 306), which is derived from the P502S gene (also referred to herein as J1-17, SEQ ID NO: 8), as described by Theobald et al., Proc. Natl. Acad. Sci. USA 92:11993-11997, 1995 with the following modifications. Mice were immunized with 100µg of P2S#12 and 120µg of an I-Ab binding peptide derived from hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and using a nylon mesh single cell suspensions prepared. Cells were then resuspended at 6 x 10<sup>6</sup> cells/ml in complete media (RPMI-1640; Gibco BRL, Gaithersburg, MD) containing 10% FCS, 2mM Glutamine (Gibco BRL), sodium pyruvate (Gibco BRL), non-essential amino acids (Gibco BRL), 2 x 10<sup>-5</sup> M 2mercaptoethanol, 50U/ml penicillin and streptomycin, and cultured in the presence of irradiated (3000 rads) P2S#12-pulsed (5mg/ml P2S#12 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7µg/ml dextran sulfate and 25µg/ml LPS for 3 days). Six days later, cells (5 x 10<sup>5</sup>/ml) were restimulated with 2.5 x 10<sup>6</sup>/ml peptide pulsed irradiated (20,000 rads) EL4A2Kb cells (Sherman et al, Science 258:815-818, 1992) and 3 x 10<sup>6</sup>/ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20U/ml IL-2. Cells continued to be restimulated on a weekly basis as described, in preparation for cloning the line.

P2S#12 line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1 x 10<sup>4</sup> cells/ well) as stimulators and A2 transgenic spleen cells

as feeders (5 x 10<sup>5</sup> cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, clones that were growing were isolated and maintained in culture. Several of these clones demonstrated significantly higher reactivity (lysis) against human fibroblasts (HLA A2.1 expressing) transduced with P502S than against control fibroblasts. An example is presented in Figure 1.

This data indicates that P2S #12 represents a naturally processed epitope of the P502S protein that is expressed in the context of the human HLA A2.1 molecule.

6.2. This Example illustrates the preparation of murine CTL lines and CTL clones specific for cells expressing the P501S gene.

This series of experiments were performed similarly to that described above. Mice were immunized with the P1S#10 peptide (SEQ ID NO: 337), which is derived from the P501S gene (also referred to herein as L1-12, SEO ID NO: 110). The P1S#10 peptide was derived by analysis of the predicted polypeptide sequence for P501S for potential HLA-A2 binding sequences as defined by published HLA-A2 binding motifs (Parker, KC, et al, J. Immunol., 152:163, 1994). P1S#10 peptide was synthesized as described in Example 4, and empirically tested for HLA-A2 binding using a T cell based competition assay. Predicted A2 binding peptides were tested for their ability to compete HLA-A2 specific peptide presentation to an HLA-A2 restricted CTL clone (D150M58), which is specific for the HLA-A2 binding influenza matrix peptide fluM58. D150M58 CTL secretes TNF in response to self-presentation of peptide fluM58. In the competition assay, test peptides at 100-200 µg/ml were added to cultures of D150M58 CTL in order to bind HLA-A2 on the CTL. After thirty minutes, CTL cultured with test peptides, or control peptides, were tested for their antigen dose response to the fluM58 peptide in a standard TNF bioassay. As shown in Figure 3, peptide P1S#10 competes HLA-A2 restricted presentation of fluM58, demonstrating that peptide P1S#10 binds HLA-A2.

Mice expressing the transgene for human HLA A2.1 were immunized as described by Theobald et al. (*Proc. Natl. Acad. Sci. USA 92*:11993-11997, 1995) with the following modifications. Mice were immunized with 62.5µg of P1S #10 and 120µg

of an I-A<sup>b</sup> binding peptide derived from Hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and single cell suspensions prepared using a nylon mesh. Cells were then resuspended at 6 x 10<sup>6</sup> cells/ml in complete media (as described above) and cultured in the presence of irradiated (3000 rads) P1S#10-pulsed (2μg/ml P1S#10 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7μg/ml dextran sulfate and 25μg/ml LPS for 3 days). Six days later cells (5 x 10<sup>5</sup>/ml) were restimulated with 2.5 x 10<sup>6</sup>/ml peptide-pulsed irradiated (20,000 rads) EL4A2Kb cells, as described above, and 3 x 10<sup>6</sup>/ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20 U/ml IL-2. Cells were restimulated on a weekly basis in preparation for cloning. After three rounds of *in vitro* stimulations, one line was generated that recognized P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat targets as shown in Figure 4.

A P1S#10-specific CTL line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1 x 10<sup>4</sup> cells/ well) as stimulators and A2 transgenic spleen cells as feeders (5 x 10<sup>5</sup> cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, viable clones were isolated and maintained in culture. As shown in Figure 5, five of these clones demonstrated specific cytolytic reactivity against P501S-transduced Jurkat A2Kb targets. This data indicates that P1S#10 represents a naturally processed epitope of the P501S protein that is expressed in the context of the human HLA-A2.1 molecule.

# EXAMPLE 7 ABILITY OF HUMAN T CELLS TO RECOGNIZE PROSTATE TUMOR POLYPEPTIDES

This Example illustrates the ability of T cells specific for a prostate tumor polypeptide to recognize human tumor.

Human CD8+ T cells were primed in vitro to the P2S-12 peptide (SEO ID NO: 306) derived from P502S (also referred to as J1-17) using dendritic cells according to the protocol of Van Tsai et al. (Critical Reviews in Immunology 18:65-75, The resulting CD8+ T cell microcultures were tested for their ability to 1998). recognize the P2S-12 peptide presented by autologous fibroblasts or fibroblasts which were transduced to express the P502S gene in a y-interferon ELISPOT assay (see Lalvani et al., J. Exp. Med. 186:859-865, 1997). Briefly, titrating numbers of T cells were assayed in duplicate on 10<sup>4</sup> fibroblasts in the presence of 3 μg/ml human β<sub>2</sub>microglobulin and 1 µg/ml P2S-12 peptide or control E75 peptide. In addition, T cells were simultaneously assayed on autologous fibroblasts transduced with the P502S gene or as a control, fibroblasts transduced with HER-2/neu. Prior to the assay, the fibroblasts were treated with 10 ng/ml y-interferon for 48 hours to upregulate class I MHC expression. One of the microcultures (#5) demonstrated strong recognition of both peptide pulsed fibroblasts as well as transduced fibroblasts in a y-interferon ELISPOT assay. Figure 2A demonstrates that there was a strong increase in the number of γ-interferon spots with increasing numbers of T cells on fibroblasts pulsed with the P2S-12 peptide (solid bars) but not with the control E75 peptide (open bars). This shows the ability of these T cells to specifically recognize the P2S-12 peptide. As shown in Figure 2B, this microculture also demonstrated an increase in the number of yinterferon spots with increasing numbers of T cells on fibroblasts transduced to express the P502S gene but not the HER-2/neu gene. These results provide additional confirmatory evidence that the P2S-12 peptide is a naturally processed epitope of the P502S protein. Furthermore, this also demonstrates that there exists in the human T cell repertoire, high affinity T cells which are capable of recognizing this epitope. These T cells should also be capable of recognizing human tumors which express the P502S gene.

#### **EXAMPLE 8**

## PRIMING OF CTL *IN VIVO* USING NAKED DNA IMMUNIZATION WITH A PROSTATE ANTIGEN

The prostate tumor antigen L1-12, as described above, is also referred to as P501S. HLA A2Kb Tg mice (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with 100 µg VR10132-P501S either intramuscularly or intradermally. The mice were immunized three times, with a two week interval between immunizations. Two weeks after the last immunization, immune spleen cells were cultured with Jurkat A2Kb-P501S transduced stimulator cells. CTL lines were stimulated weekly. After two weeks of *in vitro* stimulation, CTL activity was assessed against P501S transduced targets. Two out of 8 mice developed strong anti-P501S CTL responses. These results demonstrate that P501S contains at least one naturally processed A2-restricted CTL epitope.

#### **EXAMPLE 9**

## GENERATION OF HUMAN CTL *IN VITRO* USING WHOLE GENE PRIMING AND STIMULATION TECHNIQUES WITH PROSTATE TUMOR ANTIGEN

Using *in vitro* whole-gene priming with P501S-retrovirally transduced autologous fibroblasts (see, for example, Yee et al, *The Journal of Immunology*, 157(9):4079-86, 1996), human CTL lines were derived that specifically recognize autologous fibroblasts transduced with P501S (also known as L1-12), as determined by interferon-γ ELISPOT analysis as described above. Using a panel of HLA-mismatched fibroblast lines transduced with P501S, these CTL lines were shown to be restricted HLA-A2 class I allele. Specifically, dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by growing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, DC were infected overnight with recombinant P501S vaccinia virus at a multiplicity of infection (M.O.I) of five, and matured

overnight by the addition of 3 μg/ml CD40 ligand. Virus was inactivated by UV irradiation. CD8+ T cells were isolated using a magnetic bead system, and priming cultures were initiated using standard culture techniques. Cultures were restimulated every 7-10 days using autologous primary fibroblasts retrovirally transduced with P501S. Following four stimulation cycles, CD8+ T cell lines were identified that specifically produced interferon-γ when stimulated with P501S-transduced autologous fibroblasts. The P501S-specific activity could be sustained by the continued stimulation of the cultures with P501S-transduced fibroblasts in the presence of IL-15. A panel of HLA-mismatched fibroblast lines transduced with P501S were generated to define the restriction allele of the response. By measuring interferon-γ in an ELISPOT assay, the P501S specific response was shown to be restricted by HLA-A2. These results demonstrate that a CD8+ CTL response to P501S can be elicited.

#### **EXAMPLE 10**

## IDENTIFICATION OF A NATURALLY PROCESSED CTL EPITOPE CONTAINED WITHIN A PROSTATE TUMOR ANTIGEN

The 9-mer peptide p5 (SEQ ID NO: 338) was derived from the P703P antigen (also referred to as P20). The p5 peptide is immunogenic in human HLA-A2 donors and is a naturally processed epitope. Antigen specific CD8+ T cells can be primed following repeated *in vitro* stimulations with monocytes pulsed with p5 peptide. These CTL specifically recognize p5-pulsed target cells in both ELISPOT (as described above) and chromium release assays. Additionally, immunization of HLA-A2 transgenic mice with p5 leads to the generation of CTL lines which recognize a variety of P703P transduced target cells expressing either HLA-A2Kb or HLA-A2. Specifically, HLA-A2 transgenic mice were immunized subcutaneously in the footpad with 100 µg of p5 peptide together with 140 µg of hepatitis B virus core peptide (a Th peptide) in Freund's incomplete adjuvant. Three weeks post immunization, spleen cells from immunized mice were stimulated *in vitro* with peptide-pulsed LPS blasts. CTL activity was assessed by chromium release assay five days after primary *in vitro* 

stimulation. Retrovirally transduced cells expressing the control antigen P703P and HLA-A2Kb were used as targets. CTL lines that specifically recognized both p5-pulsed targets as well as P703P-expressing targets were identified.

Human *in vitro* priming experiments demonstrated that the p5 peptide is immunogenic in humans. Dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by culturing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, the DC were pulsed with p5 peptide and cultured with GM-CSF and IL-4 together with CD8+ T cell enriched PBMC. CTL lines were restimulated on a weekly basis with p5-pulsed monocytes. Five to six weeks after initiation of the CTL cultures, CTL recognition of p5-pulsed target cells was demonstrated.

### **EXAMPLE 11**

### EXPRESSION OF A BREAST TUMOR-DERIVED ANTIGEN IN PROSTATE

Isolation of the antigen B305D from breast tumor by differential display is described in US Patent Application No. 08/700,014, filed August 20, 1996. Several different splice forms of this antigen were isolated. The determined cDNA sequences for these splice forms are provided in SEQ ID NO: 366-375, with the predicted amino acid sequences corresponding to the sequences of SEQ ID NO: 292, 298 and 301-303 being provided in SEQ ID NO: 299-306, respectively.

The expression levels of B305D in a variety of tumor and normal tissues were examined by real time PCR and by Northern analysis. The results indicated that B305D is highly expressed in breast tumor, prostate tumor, normal prostate tumor and normal testes, with expression being low or undetectable in all other tissues examined (colon tumor, lung tumor, ovary tumor, and normal bone marrow, colon, kidney, liver, lung, ovary, skin, small intestine, stomach).

#### **EXAMPLE 12**

# ELICITATION OF PROSTATE TUMOR ANTIGEN-SPECIFIC CTL RESPONSES IN HUMAN BLOOD

This Example illustrates the ability of a prostate tumor antigen to elicit a CTL response in blood of normal humans.

Autologous dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal donors by growth for five days in RPMI medium containing 10% human serum, 50 ng/ml GMCSF and 30 ng/ml IL-4. Following culture, DC were infected overnight with recombinant P501S-expressing vaccinia virus at an M.O.I. of 5 and matured for 8 hours by the addition of 2 micrograms/ml CD40 ligand. Virus was inactivated by UV irradiation, CD8+ cells were isolated by positive selection using magnetic beads, and priming cultures were initiated in 24-well plates. Following five stimulation cycles, CD8+ lines were identified that specifically produced interferon-gamma when stimulated with autologous P501S-The P501S-specific activity of cell line 3A-1 could be transduced fibroblasts. maintained following additional stimulation cycles on autologous B-LCL transduced with P501S. Line 3A-1 was shown to specifically recognize autologous B-LCL transduced to express P501S, but not EGFP-transduced autologous B-LCL, as measured by cytotoxity assays (51Cr release) and interferon-gamma production (Interferon-gamma Elispot; see above and Lalvani et al., J. Exp. Med. 186:859-865, 1997). The results of these assays are presented in Figures 6A and 6B.

#### **EXAMPLE 13**

### IDENTIFICATION OF PROSTATE TUMOR ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of certain prostate tumor polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 372 clones were identified, and 319 were successfully sequenced. Table I presents a summary of these clones, which are shown in SEQ ID NOs:385-400. Of these sequences SEQ ID NOs:386, 389, 390 and 392 correspond to novel genes, and SEQ ID NOs: 393 and 396 correspond to previously identified sequences. The others (SEQ ID NOs:385, 387, 388, 391, 394, 395 and 397-400) correspond to known sequences, as shown in Table I.

Table I
Summary of Prostate Tumor Antigens

Known Genes	Previously identified Genes	Novel Genes
T-cell gamma chain	P504S	23379 (SEQ ID NO:389)
Kallikrein	P1000C	23399 (SEQ ID NO:392)
Vector	P501S	23320 (SEQ ID NO:386)
CGI-82 protein mRNA (23319; SEQ ID NO:385)	P503S	23381 (SEQ ID NO:390)
PSA	P510S	
Ald. 6 Dehyd.	P784P	
L-iditol-2 dehydrogenase (23376; SEQ ID NO:388)	P502S	
Ets transcription factor PDEF (22672; SEQ ID NO:398)	P706P	
hTGR (22678; SEQ ID NO:399)	19142.2, bangur.seq (22621; SEQ ID NO:396)	
KIAA0295(22685; SEQ ID NO:400)	5566.1 Wang(23404; SEQ ID NO:393)	
Prostatic Acid Phosphatase(22655; SEQ ID NO:397)	P712P	
transglutaminase (22611; SEQ ID NO:395)	P778P	
HDLBP (23508; SEQ ID NO:394)		
CGI-69 Protein(23367; SEQ ID NO:387)		
KIAA0122(23383; SEQ ID NO:391)	*	
TEEG		

CGI-82 showed 4.06 fold over-expression in prostate tissues as

compared to other normal tissues tested. It was over-expressed in 43% of prostate tumors, 25% normal prostate, not detected in other normal tissues tested. L-iditol-2 dehydrogenase showed 4.94 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 90% of prostate tumors, 100% of normal prostate, and not detected in other normal tissues tested. Ets transcription factor PDEF showed 5.55 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% prostate tumors, 25% normal prostate and not detected in other normal tissues tested. hTGR1 showed 9.11 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 63% of prostate tumors and is not detected in normal tissues tested including normal prostate. KIAA0295 showed 5.59 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% of prostate tumors, low to undetectable in normal tissues tested including normal prostate tissues. Prostatic acid phosphatase showed 9.14 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 67% of prostate tumors, 50% of normal prostate, and not detected in other normal tissues tested. Transglutaminase showed 14.84 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 30% of prostate tumors, 50% of normal prostate, and is not detected in other normal tissues tested. High density lipoprotein binding protein (HDLBP) showed 28.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% of normal prostate, and is undetectable in all other normal tissues tested. CGI-69 showed 3.56 fold over-expression in prostate tissues as compared to other normal tissues tested. It is a low abundant gene, detected in more than 90% of prostate tumors, and in 75% normal prostate tissues. The expression of this gene in normal tissues was very low. KIAA0122 showed 4.24 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 57% of prostate tumors, it was undetectable in all normal tissues tested including normal prostate tissues. 19142.2 bangur showed 23.25 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors and 100% of

normal prostate. It was undetectable in other normal tissues tested. 5566.1 Wang showed 3.31 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% normal prostate and was also over-expressed in normal bone marrow, pancreas, and activated PBMC. Novel clone 23379 showed 4.86 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in 97% of prostate tumors and 75% normal prostate and is undetectable in all other normal tissues tested. Novel clone 23399 showed 4.09 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 27% of prostate tumors and was undetectable in all normal tissues tested including normal prostate tissues. Novel clone 23320 showed 3.15 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in all prostate tumors and 50% of normal prostate tissues. It was also expressed in normal colon and trachea. Other normal tissues do not express this gene at high level.

# EXAMPLE 14 IDENTIFICATION OF PROSTATE TUMOR ANTIGENS BY ELECTRONIC SUBTRACTION

This Example describes the use of an electronic subtraction technique to identify prostate tumor antigens.

Potential prostate-specific genes present in the GenBank human EST database were identified by electronic subtraction (similar to that described by Vasmatizis et al., *Proc. Natl. Acad. Sci. USA 95*:300-304, 1998). The sequences of EST clones (43,482) derived from various prostate libraries were obtained from the GenBank public human EST database. Each prostate EST sequence was used as a query sequence in a BLASTN (National Center for Biotechnology Information) search against the human EST database. All matches considered identical (length of matching sequence >100 base pairs, density of identical matches over this region > 70%) were grouped

(aligned) together in a cluster. Clusters containing more than 200 ESTs were discarded since they probably represented repetitive elements or highly expressed genes such as those for ribosomal proteins. If two or more clusters shared common ESTs, those clusters were grouped together into a "supercluster," resulting in 4,345 prostate superclusters.

Records for the 479 human cDNA libraries represented in the GenBank release were downloaded to create a database of these cDNA library records. These 479 cDNA libraries were grouped into three groups, Plus (normal prostate and prostate tumor libraries, and breast cell lines, in which expression was desired), Minus (libraries from other normal adult tissues, in which expression was not desirable), and Other (fetal tissue, infant tissue, tissues found only in women, non-prostate tumors and cell lines other than prostate cell lines, in which expression was considered to be irrelevant). A summary of these library groups is presented in Table II.

Table II
Prostate cDNA Libraries and ESTs

Library	# of Libraries	# of ESTs
Plus	25	43,482
Normal	11	18,875
Tumor	11	21,769
Cell lines	3	2,838
Minus	166	
Other	287	

Each supercluster was analyzed in terms of the ESTs within the supercluster. The tissue source of each EST clone was noted and used to classify the superclusters into four groups: Type 1- EST clones found in the Plus group libraries only; no expression detected in Minus or Other group libraries; Type 2- EST clones found in the Plus and Other group libraries only; no expression detected in the Minus group; Type 3- EST clones found in the Plus, Minus and Other group libraries, but the

expression in the Plus group is higher than in either the Minus or Other groups; and Type 4- EST clones found in Plus, Minus and Other group libraries, but the expression in the Plus group is higher than the expression in the Minus group. This analysis identified 4,345 breast clusters (see Table III). From these clusters, 3,172 EST clones were ordered from Research Genetics, Inc., and were received as frozen glycerol stocks in 96-well plates.

<u>Table III</u> Prostate Cluster Summary

Туре	# of Superclusters	# of ESTs Ordered
1	688	677
2	2899	2484
3	85	11
4	673	0
Total	4345	3172

The inserts were PCR-amplified using amino-linked PCR primers for Synteni microarray analysis. When more than one PCR product was obtained for a particular clone, that PCR product was not used for expression analysis. In total, 2,528 clones from the electronic subtraction method were analyzed by microarray analysis to identify electronic subtraction breast clones that had high tumor vs. normal tissue mRNA. Such screens were performed using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Within these analyses, the clones were arrayed on the chip, which was then probed with fluorescent probes generated from normal and tumor prostate cDNA, as well as various other normal tissues. The slides were scanned and the fluorescence intensity was measured.

Clones with an expression ratio greater than 3 (i.e., the level in prostate tumor cDNA was at least three times the level in normal prostate cDNA) were

identified as prostate tumor-specific sequences (Table IV). The sequences of these clones are provided in SEQ ID NOs:401-453, with certain novel sequences shown in SEQ ID NOs:407, 413, 416-419, 422, 426, 427 and 450.

<u>Table IV</u>

<u>Prostate-tumor Specific Clones</u>

SEQ ID NO.	Sequence Designation	Comments
401	22545	previously identified P1000C
402	22547	previously identified P704P
403	22548	known
404	22550	known
405	22551	PSA
406	22552	prostate secretory protein 94
407	22553	novel
408	22558	previously identified P509S
409	22562	glandular kallikrein
410	22565	previously identified P1000C
411	22567	PAP
412	22568	B1006C (breast tumor antigen)
413	22570	novel
414	22571	PSA
415	22572	previously identified P706P
416	22573	novel
417	22574	novel
418	22575	novel
419	22580	novel
420	22581	PAP
421	22582	prostatic secretory protein 94
422	22583	novel
423	22584	prostatic secretory protein 94
424	22585	prostatic secretory protein 94
425	22586	known
426	22587	novel
427	22588	novel
428	22589	PAP
429	22590	known
430	22591	PSA
431	22592	known
432	22593	Previously identified P777P

433	22594	T cell receptor gamma chain
434	22595	Previously identified P705P
435	22596	Previously identified P707P
436	22847	PAP
437	22848	known
438	22849	prostatic secretory protein 57
439	22851	PAP
440	22852	PAP
441	22853	PAP
442	22854	previously identified P509S
443	22855	previously identified P705P
444	22856	previously identified P774P
445	22857	PSA
446	23601	previously identified P777P
447	23602	PSA
448	23605	PSA
449	23606	PSA
450	23612	novel
451	23614	PSA
452	23618	previously identified P1000C
453	23622	previously identified P705P

# EXAMPLE 15 FURTHER IDENTIFICATION OF PROSTATE TUMOR ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of additional prostate tumor polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 142 clones were identified and sequenced. Certain of these clones are shown in SEQ ID NOs:454-467. Of these sequences SEQ ID NOs:459-461 correspond to novel genes. The others (SEQ ID NOs:454-458 and 461-467) correspond to known sequences.

#### **EXAMPLE 16**

### FURTHER CHARACTERIZATION OF PROSTATE TUMOR ANTIGEN P710P

This Example describes the full length cloning of P710P.

The prostate cDNA library described above was screened with the P710P fragment described above. One million colonies were plated on LB/Ampicillin plates. Nylon membrane filters were used to lift these colonies, and the cDNAs picked up by these filters were then denatured and cross-linked to the filters by UV light. The P710P fragment was radiolabeled and used to hybridize with the filters. Positive cDNA clones were selected and their cDNAs recovered and sequenced by an automatic ABI Sequencer. Four sequences were obtained, and are presented in SEQ ID NOs:468-471.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the present invention is not limited except as by the appended claims.

#### **CLAIMS**

- 1. An isolated polypeptide comprising at least an immunogenic portion of a prostate tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (a) sequences recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472;
- (b) sequences that hybridize to any of the foregoing sequences under moderately stringent conditions; and
  - (c) complements of any of the sequence of (a) or (b).
- 2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing polynucleotide sequences.
- 3. An isolated polypeptide comprising a sequence recited in any one of SEQ ID NO: 108, 112, 113, 114, 172, 176, 178, 327, 329, 331, 339 and 383.
- 4. An isolated polynucleotide encoding at least 15 amino acid residues of a prostate tumor protein, or a variant thereof that differs in one or more

substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing sequences.

- 5. An isolated polynucleotide encoding a prostate tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing sequences.
- 6. An isolated polynucleotide comprising a sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472.
- 7. An isolated polynucleotide comprising a sequence that hybridizes, under moderately stringent conditions, to a sequence recited in any one of

SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472.

- 8. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 4-7.
- 9. An expression vector comprising a polynucleotide according to any one of claims 4-7.
- 10. A host cell transformed or transfected with an expression vector according to claim 9.
- 11. An expression vector comprising a polynucleotide according claim 8.
- 12. A host cell transformed or transfected with an expression vector according to claim 11.
- 13. A pharmaceutical composition comprising a polypeptide according to claim 1, in combination with a physiologically acceptable carrier.
- 14. A vaccine comprising a polypeptide according to claim 1, in combination with a non-specific immune response enhancer.
- 15. A vaccine according to claim 14, wherein the non-specific immune response enhancer is an adjuvant.

16. A vaccine according to claim 14, wherein the non-specific immune response enhancer induces a predominantly Type I response.

- 17. A pharmaceutical composition comprising a polynucleotide according to claim 4, in combination with a physiologically acceptable carrier.
- 18. A vaccine comprising a polynucleotide according to claim 4, in combination with a non-specific immune response enhancer.
- 19. A vaccine according to claim 18, wherein the non-specific immune response enhancer is an adjuvant.
- 20. A vaccine according to claim 18, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 21. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a prostate tumor protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472 or a complement of any of the foregoing polynucleotide sequences.
- 22. A pharmaceutical composition comprising an antibody or fragment thereof according to claim 18, in combination with a physiologically acceptable carrier.

23. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.

- 24. A pharmaceutical composition according to claim 23, wherein the antigen presenting cell is a dendritic cell or a macrophage.
- 25. A vaccine comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a non-specific immune response enhancer.
- 26. A vaccine according to claim 25, wherein the non-specific immune response enhancer is an adjuvant.
- 27. A vaccine according to claim 25, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 28. A vaccine according to claim 25, wherein the antigen-presenting cell is a dendritic cell.
- 29. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a polypeptide according to claim 1, and thereby inhibiting the development of a cancer in the patient.
- 30. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a polynucleotide according to claim 4, and thereby inhibiting the development of a cancer in the patient.
- 31. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antibody or antigen-

binding fragment thereof according to claim 21, and thereby inhibiting the development of a cancer in the patient.

- 32. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide according to claim 1, and thereby inhibiting the development of a cancer in the patient.
- 33. A method according to claim 32, wherein the antigen-presenting cell is a dendritic cell.
- 34. A method according to any one of claims 29-32, wherein the cancer is prostate cancer.
- 35. A fusion protein comprising at least one polypeptide according to claim 1.
- 36. A fusion protein according to claim 35, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.
- 37. A fusion protein according to claim 35, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.
- 38. A fusion protein according to claim 35, wherein the fusion protein comprises an affinity tag.
- 39. An isolated polynucleotide encoding a fusion protein according to claim 35.

40. A pharmaceutical composition comprising a fusion protein according to claim 32, in combination with a physiologically acceptable carrier.

- 41. A vaccine comprising a fusion protein according to claim 35, in combination with a non-specific immune response enhancer.
- 42. A vaccine according to claim 41, wherein the non-specific immune response enhancer is an adjuvant.
- 43. A vaccine according to claim 41, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 44. A pharmaceutical composition comprising a polynucleotide according to claim 40, in combination with a physiologically acceptable carrier.
- 45. A vaccine comprising a polynucleotide according to claim 40, in combination with a non-specific immune response enhancer.
- 46. A vaccine according to claim 45, wherein the non-specific immune response enhancer is an adjuvant.
- 47. A vaccine according to claim 45, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 48. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 40 or claim 44.

49. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a vaccine according to claim 41 or claim 45.

- 50. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (i) polynucleotides recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472; and
- (ii) complements of the foregoing polynucleotides;

  wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the prostate tumor protein from the sample.
- 51. A method according to claim 50, wherein the biological sample is blood or a fraction thereof.
- 52. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 50.
- 53. A method for stimulating and/or expanding T cells specific for a prostate tumor protein, comprising contacting T cells with one or more of:
  - (i) a polypeptide according to claim 1;
- (ii) a polypeptide encoded by a polynucleotide comprising a sequence provided in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472;
  - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); and/or

(iv) an antigen presenting cell that expresses a polypeptide of (i) or (ii);

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

- 54. An isolated T cell population, comprising T cells prepared according to the method of claim 53.
- 55. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population according to claim 54.
- 56. A method for inhibiting the development of a cancer in a patient, comprising the steps of:
- (a) incubating CD4<sup>+</sup> and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:
  - (i) a polypeptide according to claim 1;
- (ii) a polypeptide encoded by a polynucleotide comprising a sequence of any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472;
  - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); or
- (iv) an antigen-presenting cell that expresses a polypeptide of (i) or (ii);

such that T cells proliferate; and

- (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.
- 57. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating CD4<sup>+</sup> and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:

- (i) a polypeptide according to claim 1;
- (ii) a polypeptide encoded by a polynucleotide comprising a sequence of any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472;
  - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); or
- (iv) an antigen-presenting cell that expresses a polypeptide of (i) or (ii);

such that T cells proliferate;

- (b) cloning at least one proliferated cell; and
- (c) administering to the patient an effective amount of the cloned T cells, and thereby inhibiting the development of a cancer in the patient.
- 58. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with a binding agent that binds to a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (i) polynucleotides recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472; and
  - (ii) complements of the foregoing polynucleotides;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

59. A method according to claim 58, wherein the binding agent is an antibody.

- 60. A method according to claim 59, wherein the antibody is a monoclonal antibody.
- 61. A method according to claim 58, wherein the cancer is prostate cancer.
- 62. A method for monitoring the progression of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472, or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent;
- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and
- (d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
- 63. A method according to claim 62, wherein the binding agent is an antibody.
- 64. A method according to claim 63, wherein the antibody is a monoclonal antibody.

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65. A method according to claim 62, wherein the cancer is a prostate cancer.

- 66. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472, or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and
- (c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.
- 67. A method according to claim 66, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.
- 68. A method according to claim 66, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.
- 69. A method for monitoring the progression of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor

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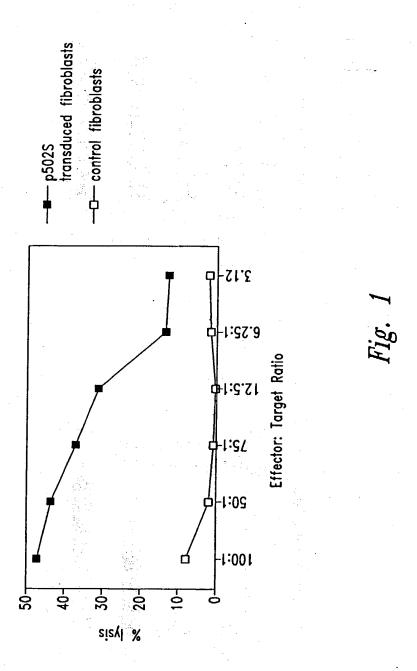
protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472, or a complement of any of the foregoing polynucleotides;

- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide;
- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and
- (d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
- 70. A method according to claim 69, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction:
- 71. A method according to claim 69, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.
  - 72. A diagnostic kit, comprising:
  - (a) one or more antibodies according to claim 21; and
  - (b) a detection reagent comprising a reporter group.
- 73. A kit according to claim 72, wherein the antibodies are immobilized on a solid support.
- 74. A kit according to claim 73, wherein the solid support comprises nitrocellulose, latex or a plastic material.

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75. A kit according to claim 72, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.

- 76. A kit according to claim 72, wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.
- 77. An oligonucleotide comprising 10 to 40 nucleotides that hybridize under moderately stringent conditions to a polynucleotide that encodes a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing polynucleotides.
- 78. A oligonucleotide according to claim 77, wherein the oligonucleotide comprises 10-40 nucleotides recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472.
  - 79. A diagnostic kit, comprising:
  - (a) an oligonucleotide according to claim 77; and
- (b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.



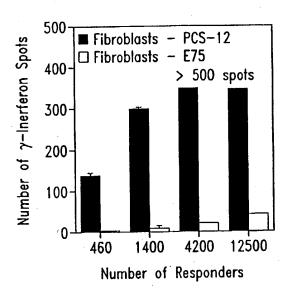


Fig. 2A

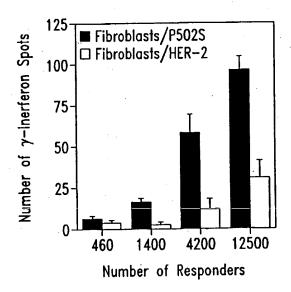
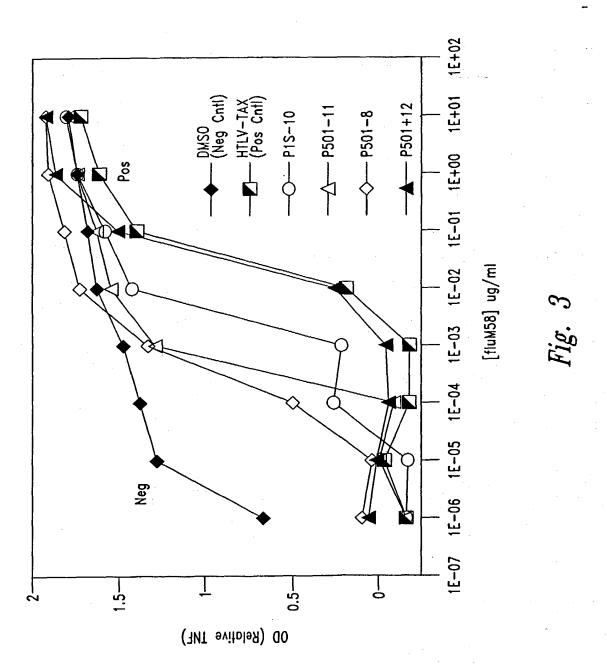
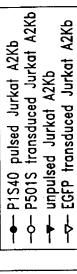


Fig. 2B



SUBSTITUTE SHEET (RULE 26)



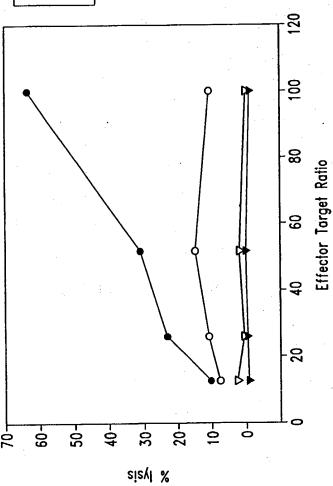
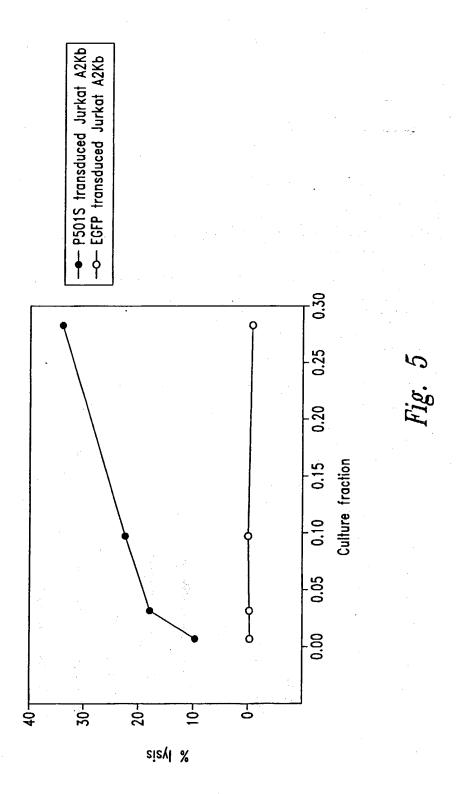


Fig. 4



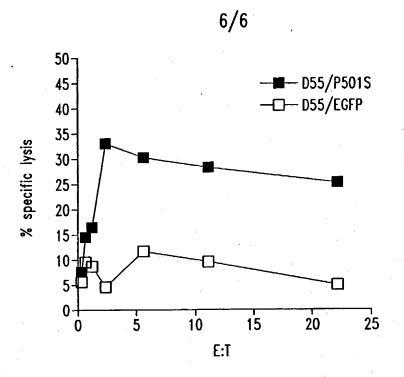


Fig. 6A

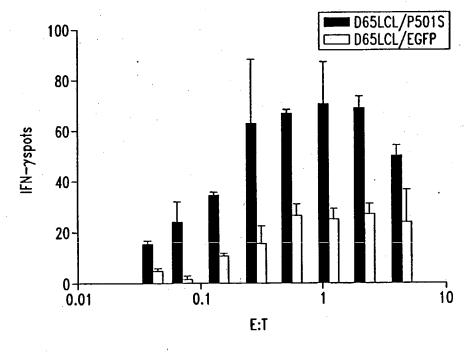


Fig. 6B

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- ottoposttop tttopopopop ottopopo				
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taangatgac actoccaaag gtggtootga cagtggcoca gatggacatg gggotcacot
caaggacaag gccaccaggt gcgggggccg aagcccacat gatccttact ctatgagcaa
                                                                         180
aatcccctgt gggggcttct ccttgaagtc cgccancagg gctcagtctt tggacccang
                                                                         240
                                                                         300
caqqtcatqq qqttqtngnc caactggggg ccncaacgca aaanggcnca gggcctcngn
                                                                         360
cacceatece angaegegge tacactnetg gaeeteeene tecaceaett teatgegetg
ttentacceg egnatnigie ecancigiti engigeenac tecancitei nggaegigeg
                                                                         420
ctacatacgc ccggantonc netcccgctt tgtccctatc cacgtnccan caacaaattt
                                                                         480
encentantg cacenattee caenttinne agnitteene nnegngette etintaaaag
                                                                         540
ggttganccc cggaaaatnc cccaaagggg gggggccngg tacccaactn ccccctnata
                                                                         600
gctgaantcc ccatnacenn gnetenatgg ancenteent tttaannaen ttetnaactt
                                                                         660
gggaanance etegneentn ecceenttaa teeeneettg enangnnent ecceenntee
                                                                         720
necennntng gentntnann enaaaaagge cennnaneaa teteetnnen eeteantteg
                                                                         780
```

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ccancecteg aaateggeen c
      <210> 10
      <211> 789
      <212> DNA
      <213> Homo sapien
      <220>
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      <222> (1) ... (789)
      <223> n = A, T, C or G
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cagtctatnt ggccagtgtg gcagctttcc ctgtggctgc cggtgccaca tgcctgtccc
                                                                         60
                                                                        120
acagtgtggc cgtggtgaca getteageeg ceeteacegg gtteacette teageeetge
agatectgee ctacacactg geetecetet accaceggga gaageaggtg tteetgeeca
                                                                        180
aataccgagg ggacactgga ggtgctagca gtgaggacag cctgatgacc agcttcctgc
                                                                        240
caggocotaa gootggagot coottooota atggacacgt gggtgotgga ggcagtggcc
                                                                        300
tgctcccacc tccacccgcg ctctgcgggg cctctgcctg tgatgtctcc gtacgtgtgg
                                                                        360
                                                                        420
tggtgggtga gcccaccgan gccagggtgg ttccgggccg gggcatctgc ctggacctcg
                                                                        480
ccatectgga tagtgettee tgetgteeca ngtggeecea tecetgttta tgggeteeat
tgtccagete agecagtetg teactgeeta tatggtgtet geegeaggee tgggtetggt
                                                                        540
                                                                        600
cccatttact ttgctacaca ggtantattt gacaagaacg anttggccaa atactcagcg
ttaaaaaaatt ccagcaacat tgggggtgga aggcctgcct cactgggtcc aactccccgc
                                                                        660
tcctgttaac cccatggggc tgccggcttg gccgccaatt tctgttgctg ccaaantnat
                                                                        720
                                                                        780
gtggctctct gctgccacct gttgctggct gaagtgcnta cngcncanct nggggggtng
                                                                        789
ggngttccc
      <210> 11
      <211> 772
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(772)
      <223> n = A, T, C or G
      <400> 11
cccacctac ccaaatatta gacaccaaca cagaaaagct agcaatggat tcccttctac
                                                                         60
                                                                        120
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accaacaggo cacatootga taaaaggtaa gaggggggtg gatcagcaaa aagacagtgo
                                                                        180
tgtgggctga ggggacctgg ttcttgtgtg ttgcccctca ggactcttcc cctacaaata
                                                                        240
                                                                        300
actiticatat qttcaaatce catqqaqqaq tqtttcatce tagaaactce catqcaagag
                                                                        360
ctacattaaa cgaagctgca ggttaagggg cttanagatg ggaaaccagg tgactgagtt
tattcagete ecaaaaacee ttetetaggt gtgtetcaae taggaggeta getgttaace
                                                                        420
ctgagcctgg gtaatccacc tgcagagtcc ccgcattcca gtgcatggaa cccttctggc
                                                                        480
                                                                        540
ctccctgtat aagtccagac tgaaaccccc ttggaaggnc tccagtcagg cagccctana
aactggggaa aaaagaaaag gacgccccan cccccagctg tgcanctacg cacctcaaca
                                                                        600
gcacagggtg gcagcaaaaa aaccacttta ctttggcaca aacaaaact ngggggggca
                                                                        660
                                                                        720
accccqqcac cccnanqqqq gttaacagga ancngggnaa cntggaaccc aattnaggca
                                                                        772
ggcccnccac cccnaatntt gctgggaaat ttttcctccc ctaaattntt tc
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      <211> 751
      <212> DNA
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      <221> misc_feature
      <222> (1) ... (751)
      <223> n = A, T, C or G
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<400> 12				
qcccaattc cagctgccac accacccacg	ataactacat	tagttcggat	otcatacaaa	60
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ttggctgtgt tggtgacgtt gtcattgcaa	cagaataaaa	gaaaggagg	attetetta	180
aagtanggtg agtcetcaaa atcegtatag	ttaataaaa	gaaaggcact	gececette	240
aagtanggtg agteeteaaa ateegtatag	testesses	catageacet	attastages	300
atggtggtgt tccacacttg agtgaagtct	teetgggaae	Cataatett	cccyacygca	360
ggcactacca gcaacgtcag ggaagtgctc	agccattgtg	gtgtacacca	aggegaceae	
agcagetgen aceteageaa tgaagatgan	gaggangatg	aagaagaacg	tcncgagggc	420
acacttgctc tcagtcttan caccatanca	gcccntgaaa	accaananca	aagaccacna	480
cneeggetge gatgaagaaa tnacceeneg	ttgacaaact	tgcatggcac	tggganccac	540
agtggcccna aaaatcttca aaaaggatgc	cccatcnatt	gaccccccaa	atgcccactg	600
ccaacagggg ctgcccacn cncnnaacga	tganccnatt	gnacaagatc	tncntggtct	660
tnatnaacht gaaccetgen tngtggetee	tgttcaggnc	cnnggcctga	cttctnaann	720
aangaacton gaagnoocca enggananno	g			751
				•
<210> 13			1	
<211> 729				* * * * * * * * * * * * * * * * * * * *
<212> DNA				
<213> Homo sapien				
· · · · · · · · · · · · · · · · · · ·				
<220>				
<221> misc feature				
<222> (1)(729)				
$\langle 223 \rangle$ n = A,T,C or G				
12237 11 11,170 02 0				
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gagecaggeg teeetetgee tgeccactea	gtggcaacac	ccaggaacta	ttttatcctt	60
tqtqqancct cagcagtncc ctctttcaga	actcantacc	aaganccctg	aacaggaggg	120
accatgcagt gcttcagctt cattaagacc	atcatcatcc	tcttcaattt	actcatcttt	180
ctgtgtggtg cagecetgtt ggcagtggge	atgatgatet	caatcaatca	gocatecttt	240
ctgaagatet tegggeeact gtegteeagt	accegggege	ttatcaacat	ggcatecttc	300
etgaagatet tegggeeact gregteeagt	gccacgcagc	tagactacta	taatacteea	360
ctcatcgcag ccggcgttgt ggtcttagct	ttattatta	testestest	ettestteet	420
actgagagca agtgtgccct cgtgacgttc	ttetteatee	rectededat	ttootgogt	480
gaggttgcaa tgctgtggtc gccttggtgt	acaccacaat	ggccgagcac	treetgaegt	540
tgctggtaat gcctgccatc aanaaagat	tatgggttcc	caggaanact	teacteaagt	600
gttggaacac caccatgaaa gggctcaagt	getgtggett	cnnccaacta	Lacygatttt	660
gaagantcac ctacttcaaa gaaaanagtg	cctttccccc	atttctgttg	caattgacaa	
acgicccaa cacagccaat igaaaaccig	cacccaaccc	aaangggtee	ccaaccanaa	720
attnaaggg				729
	<u>.</u>			
<210> 14				
<211> 816				
<212> DNA			•	
<213> Homo sapien				
<220>				
<221> misc_feature				
<222> (1)(816)				
$\langle 223 \rangle$ n = A,T,C or G				
		*		
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tottcoctoa aggosttota otaccagege	gggatgctct	ccttgcagag	tcctgtgtct	120
ggcaggtcca cgcagtgccc tttgtcactg	gggaaatgga	tgcgctggag	ctcgtcaaag	180
ccactcgtgt atttttcaca ggcagcctcg	tccgacgcgt	coggocagtt	gggggtatct	240
tcacactcca ggaaactgtc natgcagcag	ccattactac	agcggaactg	ggtgggctga	300
cangtgccag agcacactgg atggcgcctt	tccatonnan	agaccetana	ggaaagtccc	360
tgancccan anctgcctct caaangcccc	accttgcaca	CCCCGacaga	ctagaatgga	420
atcttcttcc cgaaaggtag ttnttcttgt	tacccaance	ancocontaa	acaaactctt	480
gcanatotgo toognggggg tontantace	ancatagase	aagaacccca	adchacassa	540
caancttgtt tggatncgaa gcnataatct	notattotes	ttaataasas	ggengegaae	600

7

```
etginnanct tragneening greetening griginneting aacetaaten cennicaact
gggacaaggt aantngcont cotttnaatt cocnanentn coccetggtt tggggttttn
                                                                        720
                                                                        780
cnenetecta ecceagaaan neegtgttee ecceeaacta qqqqeenaaa cennttntte
                                                                        816
cacaaccetn ccccacccac gggttengnt ggttng
      <210> 15
      <211> 783
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(783)
      <223> n = A,T,C or G
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                                                                        120
aagacccaaa ccaggtggaa ctgtggggac tcaaggaang cacctacctg ttccagctga
                                                                        180
                                                                        240
cagtgactag ctcagaccac ccagaggaca cggccaacgt cacagtcact gtgctgtcca
ccaagcagac agaagactac tgcctcgcat ccaacaangt gggtcgctgc cggggctctt
                                                                        300
teccaegetg gtactatgae eccaeggage agatetgeaa gagtttegtt tatggagget
                                                                        360
gcttgggcaa caagaacaac taccttcggg aagaagagtg cattctancc tgtcngggtg
                                                                        420
tgcaaggtgg gcctttgana ngcanctctg gggctcangc gactttcccc cagggcccct
                                                                        480
ccatggaaag gcgccatcca ntgttctctg gcacctgtca gcccacccag ttccgctgca
                                                                        540
neaatggetg etgeatenae anttteetng aattgtgaca acacceccca ntgeecccaa
                                                                        600
                                                                        660
ccctcccac aaagcttccc tgttnaaaaa tacnccantt ggcttttnac aaacncccgg
cncctccntt ttccccnntn aacaaagggc nctngcnttt gaactgcccn aacccnggaa
                                                                        720
tetneening aaaaantnee eeceetggtt cetinaanee eeteenenaa anetneeece
                                                                        780
                                                                        783
CCC
      <210> 16
      <211> 801
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(801)
      <223> n = A, T, C or G
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                                                                         60
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agetgattga ageaaceete taetttttgg tegtgageet tttgettggt geaggtttea
                                                                        120
ttggctgtgt tggtgacgtt gtcattgcaa cagaatgggg gaaaggcact gttctctttg
                                                                        180
aagtagggtg agtcctcaaa atccgtatag ttggtgaagc cacagcactt gagccctttc
                                                                        240
                                                                        300
atggtggtgt tccacacttg agtgaagtct tcctgggaac cataatcttt cttgatggca
                                                                        360
ggcactacca gcaacgtcag gaagtgctca gccattgtgg tgtacaccaa ggcgaccaca
gcagctgcaa cctcagcaat gaagatgagg aggaggatga agaagaacgt cncgagggca
                                                                        420
cacttgctct ccgtcttagc accatagcag cccangaaac caagagcaaa gaccacaacg
                                                                        480
congotgoga atgaaagaaa ntacccacgt tgacaaactg catggccact ggacgacagt
                                                                        540
                                                                        600
tggcccgaan atcttcagaa aagggatgcc ccatcgattg aacacccana tgcccactgc
cnacaggget geneenenen gaaagaatga geeattgaag aaggatente ntggtettaa
                                                                        660
tqaactqaaa contqoatqq tqqcccctqt tcaqqqctct tqqcaqtqaa ttctqanaaa
                                                                        720
aaggaacngc ntnagccccc ccaaangana aaacaccccc gggtgttgcc ctgaattggc
                                                                        780
                                                                        801
ggccaaggan ccctgccccn g
      <210> 17
      <211> 740
      <212> DNA
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<213> Homo sapien

```
<220>
      <221> misc feature
      <222> (1)...(740)
      <223> n = A, T, C \text{ or } G
      <400> 17
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                                                                          60
cctttqtqqa qcctcaqcaq ttccctcttt caqaactcac tqccaaqagc cctqaacaqq
                                                                         120
                                                                         180
agecaccatg cagtgettea getteattaa gaccatgatg atcetettea atttgeteat
ctttctgtgt ggtgcagccc tgttggcagt gggcatctgg gtgtcaatcg atggggcatc
                                                                         240
ctttctqaag atcttcgggc cactgtcgtc cagtgccatg cagtttgtca acgtgggcta
                                                                         300
cttcctcatc gcagccqqcq ttqtqqtctt tgctcttqqt ttcctqqqct gctatqqtqc
                                                                         360
taagacggag agcaagtgtg ccctcgtgac gttcttcttc atcctcctcc tcatcttcat
                                                                         420
tgctgaagtt gcagctgctg tggtcgcctt ggtgtacacc acaatggctg aaccattect
                                                                         480
gacgttgctg gtantgcctg ccatcaanaa agattatggg ttcccaggaa aaattcactc aantntggaa caccnccatg aaaagggctc caatttctgn tggcttcccc aactataccg
                                                                         540
                                                                         600
gaattttgaa aganteneee taetteeaaa aaaaaanant tgeetttnee ecenttetgt
                                                                         660
tgcaatgaaa acntcccaan acngccaatn aaaacctgcc cnnncaaaaa ggntcncaaa
                                                                         720
                                                                         740
caaaaaaant nnaagggttn
      <210> 18
      <211> 802
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (802)
      <223> n = A, T, C or G
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caaggtette cagetgeege acattaegea gggcaagage etceageaac actgeatatg
                                                                         120
                                                                         180
ggatacactt tactttagca gccagggtga caactgagag gtgtcgaagc ttattcttct
gagectetgt tagtggagga agatteeggg etteagetaa gtagteageg tatgteecat
                                                                         240
aagcaaacac tgtgagcagc cggaaggtag aggcaaagtc actctcagcc agctctctaa
                                                                         300
cattgggcat gtccagcagt tctccaaaca cgtagacacc agnggcctcc agcacctgat
                                                                         360
ggatgagtgt ggccagcgct gcccccttgg ccgacttggc taggagcaga aattgctcct
                                                                         420
ggttctgccc tgtcaccttc acttccgcac tcatcactgc actgagtgtg ggggacttgg
                                                                         480
                                                                         540
qctcaqqatq tccaqaqacq tqqttccqcc ccctcnctta atgacaccqn ccanncaacc
                                                                         600
gteggetece geegantgng ttegtegtne etgggteagg gtetgetgge enetacttge
aancttcgtc nggcccatgg aattcaccnc accggaactn gtangatcca ctnnttctat
                                                                         660
aaccggncgc caccgcnnnt ggaactccac tettnttncc tttacttgag ggttaaggtc
                                                                         720
accettnneg ttacettggt ccaaacentn centgtgteg anatngtnaa tenggneena
                                                                         780
                                                                         802
tnccancene atangaagee ng
      <210> 19
      <211> 731
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(731)
      <223> n = A, T, C or G
      <400> 19
cnaagettee aggtnaeggg eegenaance tgaceenagg tancanaang eagnengegg
                                                                           60
gageceaeeg teaegnggng gngtetttat nggaggggge ggagecaeat enetggaent
                                                                         120
entgacecca acteceence nencantgea gtgatgagtg cagaactgaa ggtnaegtgg
                                                                         180
caqqaaccaa gancaaanne tgeteennte caagteggen nagggggegg ggetggecae
                                                                         240
geneateent enagtgetgn aaageeeenn eetgtetaet tgtttggaga aengennnga
                                                                         300
```

```
catgeceagn gttanataac nggengagag tnantttgee tetecettee qgetgegean
                                                                          360
congtntqct tagngqacat aacctgacta cttaactgaa cccnnqaatc tnccnccct
                                                                          420
                                                                          480
ccactaagct cagaacaaaa aacttcgaca ccactcantt gtcacctgnc tgctcaagta
aagtgtaccc catnoccaat gtntgctnga ngctctgncc tgcnttangt tcggtcctgg
                                                                          540
gaagacctat caattnaagc tatgtttctg actgcctctt gctccctgna acaancnacc
                                                                          600
ennennteca agggggggne ggeeceaat ceeeceaace ntnaattnan tttanceen
                                                                          660
ccccnggcc cggcctttta cnancntcnn nnacngggna aaaccnnnqc tttncccaac
                                                                         720
nnaatccncc t
                                                                         731
      <210> 20
      <211> 754
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(754)
      <223> n = A, T, C or G
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                                                                          60
caacccctc ntccaaatnn centtteegg gngggggtte caaacccaan ttanntttgg
                                                                         120
annttaaatt aaatnttnnt tggnggnnna anccnaatgt nangaaagtt naacccanta
                                                                         180
tnancttnaa tneetggaaa cengtngntt eeaaaaatnt ttaaccetta anteceteeg
                                                                         240
aaatngttna nggaaaaccc aanttctcnt aaggttgttt gaaggntnaa tnaaaanccc
                                                                         300
nnccaattgt ttttngccac gcctgaatta attggnttcc gntgttttcc nttaaaanaa
                                                                         360
ggnnancccc ggttantnaa tccccccnnc cccaattata ccganttttt ttngaattgg
                                                                         420
ganceenegg gaattaaegg ggnnnnteee tnttgggggg enggnneece eeenteggg ggttngggne aggnennaat tgtttaaggg teegaaaaat eeeteenaga aaaaaanete
                                                                         480
                                                                         540
ccaggntgag nntngggttt ncccccccc canggcccct ctcgnanagt tggggtttgg
                                                                         600
ggggcctggg attttntttc ccctnttncc tcccccccc ccnggganag aggttngngt
                                                                         660
                                                                         720
tttgntcnnc ggccccnccn aaganctttn ccganttnan ttaaatccnt gcctnggcga
agtccnttgn agggntaaan ggccccctnn cggg
                                                                         754
      <210> 21
      <211> 755
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (755)
      <223> n = A, T, C or G
      <400> 21
                                                                          60
atcancecat gacceenaae nngggacene teanceggne nnnenaeene eggeenatea
nngtnagnne actnennttn nateaeneee encenactae gecenenane enaegeneta
                                                                         120
nncanatnee actganngeg egangtngan ngagaaanet nataccanag neaccanaen
                                                                         180
ccagctgtcc nanaangcct nnnatacngg nnnatccaat ntgnancctc cnaaqtattn
                                                                         240
nnenneanat gatttteetn anecgattae centneecee taneceetee eececaaena
                                                                         300
egaaggenet ggneenaagg nngegnenee eegetagnte eeenneaagt eneneneeta
                                                                         360
aacteancen nattaenege ttentgagta teacteceeg aateteacee tacteaacte
                                                                         420
aaaaanatcn gatacaaaat aatncaagcc tgnttatnac actntgactg ggtctctatt
                                                                         480
ttagnggtee ntnaanente etaataette eagtetneet tenecaattt eenaangget
                                                                         540
ctttcngaca gcatnttttg gttcccnntt gggttcttan ngaattgccc ttcntngaac
                                                                         600
gggctcntct tttccttcgg ttancctggn ttcnnccggc cagttattat ttcccntttt
                                                                         660
aaattentne entttanttt tggenttena aacceeegge ettgaaaaeg geeeeetggt
                                                                         720
                                                                         755
aaaaggttgt tttganaaaa tttttgtttt gttcc
      <210> 22
      <211> 849
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<212> DNA

```
<213> Homo sapien
      <220>
      <221> misc feature
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      <223> n = A, T, C or G
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                                                                           60
acgetnggan taangegace eganttetag ganneneest aaaateanae tgtgaagatn
                                                                         120
atcctgnnna cggaanggtc accggnngat nntgctaggg tgnccnctcc cannnenttn
                                                                         180
cataacteng nggccetgee caccacette ggeggeeeng ngneegggee egggteattn
                                                                         240
gnnttaaccn cactnngcna neggttteen neecenneng accenggega teeggggtne
                                                                         300
tetgtettee cetgnagnen anaaantggg ceneggneee etttaceeet nnacaageea engeenteta neenengeee eeeeteeant nngggggaet geenannget eegttnetng
                                                                         360
                                                                         420
nnacecennn gggtneeteg gttgtegant enacegnang ceanggatte enaaggaagg
                                                                         480
tgcgttnttg gccctaccc ttcgctncgg nncacccttc ccgacnanga nccgctcccg
                                                                         540
enennegning ecteneeteg caacaceege netentengt negginnece ecceaceege
                                                                         600
necetenene ngnegnanen eteeneenee gteteannea ecaceegee eegecaggee
                                                                         660
ntcanccach ggnngachng nagenennte geneegegen gegneneett egeenengaa
                                                                         720
ctncntcngg ccantnncgc tcaanconna cnaaacgccg ctgcgcggcc cgnagcgncc
                                                                         780
necteenega gteeteeegn etteenacee angnntteen egaggaeaen nnaceeegee
                                                                         840
nncangcgg
                                                                         849
      <210> 23
      <211> 872
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (872)
      <223> n = A, T, C or G
      <400> 23
gogcaaacta tacttogoto quactogtgo gootogotuo tottttooto ogcaaccatq
                                                                          60
tetgacnane eegattngge ngatatenan aagntegane agtecaaaet gantaacaca
                                                                         120
cacacnenan aganaaatee netgeettee anagtanaen attgaaenng agaaeeange
                                                                         180
nggcgaateg taatnaggeg tgegeegeea atntgtenee gtttattntn ceagentene
                                                                         240
ctnccnaccc tacntetten nagetgtenn acceetngtn egnaceeece naggteggga
                                                                         300
tegggtttnn nntgacegng ennecectee eccenteeat naeganeene eegcaceaee
                                                                         360
nanngenege necessanet ettegeenee etgteetnin eeeetginge etggenengn
                                                                         420
accgcattga ccctcgccnn ctncnngaaa ncgnanacgt ccgggttgnn annancgctg
                                                                         480
tgggnnngcg tctgcnccgc gttccttccn ncnncttcca ccatcttcnt tacngggtct
                                                                         540
conceents tennneache cetgggacge intectnige ecceetinae tecceecti
                                                                         600
cgncgtgncc cgnccccacc ntcatttnca nacgntcttc acaannnect ggntnnctcc
                                                                         660
cnancingnen gteancenag ggaagggngg ggnneenntg nttgaegttg nggngangte
                                                                         720
egaanantee tencentean enetaceest egggegnnet etengttnee aacttaneaa
                                                                         780
ntetececcg ngngenente teagectene ceneceenet etetgeantg tnetetgete
                                                                         840
tnaccnntac gantnttcgn cnccctcttt cc
                                                                         872
      <210> 24
      <211> 815
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(815)
      <223> n = A, T, C or G
      <400> 24
```

.60

```
gcatgcaagc ttgagtattc tatagngtca cctaaatanc ttggcntaat catggtcnta
 nctgncttcc tgtgtcaaat gtatacnaan tanatatqaa tctnatntqa caaqannqta
                                                                           120
 tentneatta gtaacaantg tnntgteeat eetgtengan canatteeca tnnattnegn
                                                                           180
 egeattenen geneantatn taatngggaa ntennntnnn neacenneat etatentnee
                                                                           240
 geneectgae tggnagagat ggatnantte tnntntgace nacatgttea tettggattn
                                                                           300
 aananceece egengneeae eggtingning enageeninte ecaagacete etgiqqaqqt
                                                                           360
 aacctgcgtc aganncatca aacntgggaa acccgcnncc angtnnaaqt ngnnncanan
                                                                           420
 gatecegtee aggnttnace atceettene agegeeeet tingtgeett anagngnage
                                                                           480
 gtgtccnanc enctcaacat ganacgegee agneeanceg caattnggea caatgtegne
                                                                           540
 gaacccccta gggggantna thcaaanccc caggattgtc chchcangaa atcccncanc
                                                                           600
 ccenccetae cennetttgg gacngtgace aanteeegga gtneeagtee ggeengnete
                                                                           660
 ecceaceggt nncentgggg gggtgaanet engnnteane engnegaggn ntegnaagga
                                                                           720
 accggneetn ggnegaanng anenntenga agngeenent egtataacce ecceteneca
                                                                           780
nccnacngnt agntccccc cngggtncgg aangg
                                                                           815
       <210> 25
       <211> 775
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1) ... (775)
      <223> n = A, T, C or G
      <400> 25
ecgagatgte tegeteegtg geettagetg tgetegeet actetetet tetggeetgg
                                                                            60
aggetateca gegtaeteca aagatteagg tttaeteacg teatecagea gagaatggaa
                                                                           120
agtcaaattt cctgaattgc tatgtgtctg ggtttcatcc atccgacatt gaanttgact
                                                                           180
tactgaagaa tgganagaga attgaaaaag tggagcattc agacttgtct ttcagcaagg
                                                                           240
actggtcttt ctatctcntg tactacactg aattcacccc cactgaaaaa gatgagtatg
                                                                           300
cctgccgtgt gaaccatgtg actttgtcac agcccaagat agttaagtgg gatcgagaca
                                                                           360
tgtaagcagn cnncatggaa gtttgaagat gccgcatttg gattggatga attccaaatt ctgcttgctt gcnttttaat antgatatgc ntatacaccc taccctttat gnccccaaat
                                                                           420
                                                                           480
tgtaggggtt acatnantgt tenentngga catgatette etttataant cencentteg
                                                                           540
aattgcccgt cncccngttn ngaatgtttc cnnaaccacg gttggctccc ccaggtcncc
                                                                           600
tottacggaa gggcctgggc cnctttncaa ggttggggga accnaaaatt toncttntgc
                                                                           660
conceencea enntettgng nneneanttt ggaaccette enatteeeet tggeetenna
                                                                           720
nccttnncta anaaaacttn aaancgtngc naaanntttn acttccccc ttacc
                                                                           775
      <210> 26
      <211> 820
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (820)
      <223> n = A, T, C or G
anattantac agtgtaatct tttcccagag gtgtgtanag ggaacggggc ctagaggcat
                                                                            60
cccanagata nettatanca acagtgettt gaccaagage tgetgggeac attteetgea
                                                                           120
gaaaaggtgg cggtccccat cactcctcct ctcccatagc catcccagag gggtgagtag
                                                                           180
ccatcangce tteggtggga gggagtcang gaaacaacan accacagage anacagacea ntgatgacea tgggcgggag cgageetett ecetgnaceg gggtggeana nganageeta
                                                                           240
                                                                           300
nctgagggt cacactataa acgttaacga ccnagatnan cacctgcttc aaqtgcaccc
                                                                           360
ttectacetg acnaecagng acennnaact gengeetggg gaeagenetg ggancageta
                                                                           420
acnnageact cacetgeece eccatggeeg thegenteec tggteetgne aagggaaget
                                                                           480
ccctgttgga attncgggga naccaaggga nccccctcct ccanctgtga aggaaaaann
                                                                           540
gatggaattt tnecetteeg geennteece tetteettta eacgeoceet nntactente
                                                                           600
tecetetntt nteetgnene aettttnace cennnattte eettnattga teggannetn
                                                                           660
```

```
ganattecae thnegeethe entenateng naanachaaa nacthtetha ecengggat
                                                                             720
 gggnnceteg ntcatcetet etttttenet acencenntt etttgeetet cettngatea
780tccaacente gntggeentn ecceccennn teetttneec
820
       <210> 27
       <211> 818
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1) ... (818)
       <223> n = A, T, C or G
       <400> 27
 tetgggtgat ggeetettee teeteaggga cetetgaetg etetgggeea aagaatetet
                                                                              60
                                                                             120
 tgtttcttct ccgagcccca ggcagcggtg attcagccct gcccaacctg attctgatga
 ctgcggatgc tgtgacggac ccaaggggca aatagggtcc cagggtccag ggaggggcgc
                                                                             180
 ctgctgagca cttccgcccc tcaccctgcc cagcccctgc catgagctct gggctgggtc
                                                                             240
 tecqueteca gggttetget ettecangea ngccancaag tggcgetggg ccacactgge
                                                                             300
 ttetteetge ecentecetg getetgante tetgtettee tgteetgtge angeneettg
                                                                             360
 gateteagtt teeetenete anngaactet gtttetgann tetteantta actntgantt
                                                                             420
 tatnaccnan tggnetgtne tgtennactt taatgggeen gaeeggetaa teeeteete
                                                                             480
                                                                             540
 netecettee anttennna accegettee ententetee centaneceg cengggaane
 ctcctttgcc ctnaccangg gccnnnaccg cccntnnctn ggggggcnng gtnnctncnc ctgntnnccc cnctcncnnt tncctcgtcc cnncnncgcn nngcannttc ncngtcccnn
                                                                             600
                                                                             660
 tnnetetten ngtntegnaa ngntenentn tnnnnngnen ngntnntnen teeetetene
                                                                             720
                                                                             780
 conntquang touttonno nengoneece nonnennon nggonotonn tetnenenge
                                                                             818
 ccennecece ngnattaagg ceteenntet ceggeene
       <210> 28
       <211> 731
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(731)
       <223> n = A, T, C or G
       <400> 28
 aggaagggcg gagggatatt gtangggatt gagggatagg agnataangg gggaggtgtg
                                                                              60
                                                                             120
 teceaacatg anggtgnngt tetetittga angagggttg ngtttttann cenggtgggt
 gattnaaccc cattgtatgg agnnaaaggn tttnagggat ttttcggctc ttatcagtat
                                                                             180
                                                                             240
 ntanatteet qtnaategga aaatnatntt tennenggaa aatnttgete ceateegnaa
 attnetcccg ggtagtgcat nttngggggn engecangtt teccaggetg ctanaategt
                                                                             300
 actaaagntt naagtgggan tncaaatgaa aacctnncac agagnatcon tacccgactg
                                                                             360
 tnnnttneet tegeeetntg aetetgenng ageceaatae eenngngnat gteneeengn nnngegnene tgaaannnne tegnggetnn ganeateang gggtttegea teaaaagenn
                                                                             420
                                                                             480
 cgtttencat naaggeactt tngcctcate caacenetng cectenneca tttngccgte
                                                                             540
 ngqttcncct acgctnntng cncctnnntn ganattttnc ccgcctnggg naancetect
                                                                             600
 gnaatgggta gggnettnte ttttnacenn gnggtntaet aatennetne acgentnett
                                                                             660
                                                                             720
 tetenaceee ecceetttt caateeeane ggenaatggg gteteeeenn egangggggg
                                                                             731
 nnncccannc c
       <210> 29
       <211> 822
       <212> DNA
```

<220>

<213> Homo sapien

```
<221> misc_feature
       <222> (1) ... (822)
       <223> n = A, T, C or G
       <400> 29
actagtccag tgtggtggaa ttccattgtg ttggggncnc ttctatgant antnttagat
                                                                             60
egeteanace teacaneete cenaenange etataangaa nannaataga netgtnennt
                                                                            120
aththtache teatanneet ennnaceeae teeetettaa eeentaetgt geetatngen
                                                                            180
tnnctantet ntgccgcctn cnanccaccn gtgggccnac cncnngnatt ctcnatetec
                                                                            240
tenecatnin gectananta ngineatace etatacetae necaatgeta nnnetaanen
                                                                            300
tocatnantt annntaacta coactgacht ngactttene atnanctect aatttgaate
                                                                            360
tactetgact eccaengeet annnattage anentecece nacnatntet caaccaaate
                                                                            420
ntcaacaacc tatctanctg ttcnccaacc nttncctccg atccccnnac aaccccctc
                                                                            480
ccaaataccc nccacctgac ncctaacccn caccatcccg gcaagccnan ggncatttan ccactggaat cacnatngga naaaaaaaac ccnaactctc tancncnnat ctccctaana
                                                                            540
                                                                            600
aatneteetn naatttaetn neantneeat caaneecaen tgaaaennaa eeeetgtttt
                                                                            660
tanatecett etttegaaaa eenaeeettt annneeeaae etttngggee eeceenetne
                                                                            720
ccnaatgaag gncncccaat cnangaaacg nccntgaaaa ancnaggcna anannntccg
                                                                            780
canatcetat ccettanttn ggggnecett necengggee ee
                                                                            822
       <210> 30
      <211> 787
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
      <222> (1) ... (787)
      <223> n = A, T, C \text{ or } G
      <400> 30
cggccgcctg ctctggcaca tgcctcctga atggcatcaa aagtgatgga ctgcccattg
                                                                             60
ctagagaaga cottototo tactgtoatt atggagccot gcagactgag ggotocoott
                                                                           120
gtctgcagga tttgatgtct gaagtcgtgg agtgtggctt ggagctcctc atctacatna gctggaagcc ctggagggcc tctctcgcca gcctcccct tctctccacg ctctccangg
                                                                            180
                                                                           240
acaccagggg ctccaggcag cccattattc ccagnangac atggtgtttc tccacgcgga
                                                                           300
cccatgggc ctgnaaggcc agggtctcct ttgacaccat ctctcccgtc ctgcctggca
                                                                           360
ggccgtggga tccactantt ctanaacggn cgccaccncg gtgggagctc cagcttttgt
                                                                            420
tecenttaat gaaggttaat tgenegettg gegtaateat nggteanaac tnttteetgt
                                                                           480
gtgaaattgt ttntcccctc ncnattccnc ncnacatacn aacccggaan cataaagtgt
                                                                           540
taaagcctgg gggtngcctn nngaatnaac tnaactcaat taattgcgtt ggctcatggc
                                                                            600
ccgctttccn ttcnggaaaa ctgtcntccc ctgcnttnnt gaatcggcca ccccccnggg
                                                                           660
aaaageggtt tgenttttng ggggnteett cenetteece eetenetaan eeetnegeet
                                                                           720
                                                                           780
eggtegttne nggtngeggg gaangggnat nnnetecene naagggggng agnnngntat
ccccaaa
                                                                           787
      <210> 31
      <211> 799
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(799)
      <223> n = A, T, C or G
      <400> 31
ttttttttt ttttttggc gatgctactg tttaattgca ggaggtgggg gtgtgtgtac
                                                                            60
catgtaccag ggctattaga agcaagaagg aaggagggag ggcagagcgc cctgctgagc
                                                                           120
aacaaaggac teetgeagee ttetetgtet gtetettgge geaggeacat ggggaggeet
                                                                           180
eccgcagggt gggggccacc agtccagggg tgggagcact acanggggtg ggagtgggtg
                                                                           240
gtggctggtn cnaatggcct gncacanatc cctacgattc ttgacacctg gatttcacca
                                                                           300
```

```
ggggaccttc tgttctccca nggnaacttc ntnnatctcn aaagaacaca actgtttctt
                                                                            360
cngcanttct ggctgttcat ggaaagcaca ggtgtccnat ttnggctggg acttggtaca
                                                                            420
tatggttccg gcccacctct cccntcnaan aagtaattca ccccccccn ccntctnttg
                                                                            480
cctgggcct taantaccca caccggaact canttantta ttcatcttng gntgggcttg
                                                                            540
ntnatencen cetgaangeg ecaagttgaa aggeeaegee gtneeenete eccatagnan
                                                                            600
nttttnnent canctaatge ceeecengge aacnatecaa teeeceecen tgggggeece
                                                                            660
ageccange eccegneteg ggnnneengn enegnantee ecaggnetee ecantengne
                                                                            720
connigence ecceptacea gaacanaagg ntingageene egeanninnin nggtinenae
                                                                            780
                                                                            799
ctcgccccc ccnncqnng
       <210> 32
       <211> 789
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1) ... (789)
       <223> n = A, T, C or G
       <400> 32
tttttttt tttttttt
                                                                             60
ttttnccnag ggcaggttta ttgacaacct cncgggacac aancaggctg gggacaggac
                                                                            120
                                                                            180
ggcaacaggc teeggeggeg geggeggegg cectacetge ggtaccaaat ntgcageete
egeteeeget tgatntteet etgeagetge aggatgeent aaaacaggge eteggeentn
                                                                            240
ggtgggcacc ctgggatttn aatttccacg ggcacaatgc ggtcgcancc cctcaccacc nattaggaat agtggtntta cccnccnccg ttggcncact cccntggaa accacttntc
                                                                            300
                                                                            360
qcqqctccqq catctqqtct taaaccttqc aaacnctqqq qccctctttt tqqttantnt
                                                                            420
ncongocaca atcatnacto agactgono gggetgoco caaaaaanon coccaaaaco
                                                                            480
ggnecatgte ttnneggggt tgetgenatn tneateacet eeegggenea neaggneaae
                                                                            540
ccaaaagttc ttgnggcccn caaaaaanct ccggggggnc ccagtttcaa caaagtcatc
                                                                            600
ccccttggcc cccaaatcct ccccccgntt nctgggtttg ggaacccacg cctctnnctt
                                                                            660
tggnnggcaa gntggntccc ccttcgggcc cccggtgggc ccnnctctaa ngaaaacncc
                                                                            720
ntectninea ceatecece inginaegne tancaangna teeettttt tanaaaeggg
                                                                            780
                                                                            789
cccccncg
      <210> 33
      <211> 793
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(793)
      <223> n = A, T, C or G
      <400> 33
qacaqaacat qttqqatqqt qqaqcacctt tctatacqac ttacaqqaca qcaqatqqqq
                                                                             60
aattcatggc tgttggagca atanaacccc agttctacga gctgctgatc aaaggacttg
                                                                            120
                                                                            180
gactaaagto tgatgaactt cocaatcaga tgagcatgga tgattggcca gaaatgaana
agaagttige agatgtattt geaaagaaga egaaggeaga giggtgicaa atettigaeg
                                                                            240
                                                                            300
gcacagatgc ctgtgtgact ccggttctga cttttgagga ggttgttcat catgatcaca
                                                                            360
acaangaacg gggctcgttt atcaccantg aggagcagga cgtgagcccc cgccctgcac
ctctgctgtt aaacacccca gccatccctt ctttcaaaag ggatccacta cttctagagc
                                                                            420
ggncgccacc gcggtggagc tccagctttt gttcccttta gtgagggtta attgcgcgct tggcgtaatc atggtcatan ctgtttcctg tgtgaaattg ttatccgctc acaattccac acaacatacg anccggaagc atnaaatttt aaagcctggn ggtngcctaa tgantgaact
                                                                            480
                                                                           540
                                                                            600
nacteacatt aattggettt gegeteactg eccgetttee agteeggaaa acctgteett
                                                                            660
qccaqctqcc nttaatgaat cnggccaccc cccggggaaa aggcnqtttq cttnttqqqq
                                                                            720
                                                                           780
egenettece getttetege tteetgaant cetteeece ggtetttegg ettgeggena
                                                                            793
acggtatcna cct
```

```
<210> 34
       <211> 756
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(756)
       \langle 223 \rangle n = A,T,C or G
       <400> 34
gccgcgaccg gcatgtacga gcaactcaag ggcgagtgga accgtaaaag ccccaatctt
                                                                          60
ancaagtgcg gggaanagct gggtcgactc aagctagttc ttctggagct caacttcttg
                                                                         120
ccaaccacag ggaccaaget gaccaaacag cagetaatte tggcccgtga catactggag
                                                                         180
ateggggeee aatggageat cetaegeaan gacateceet cettegageg ctacatggee
                                                                        240
cageteaaat getaetaett tgattaeaan gageagetee eegagteage etatatgeae
                                                                         300
cagetettgg geeteaacet cetetteetg etgteecaga acegggtgge tgantnecae
                                                                        360
acgganttgg ancggctgcc tgcccaanga catacanacc aatgtctaca tcnaccacca
                                                                         420
gtgtcctgga gcaatactga tgganggcag ctaccncaaa gtnttcctgg ccnaqqqtaa
                                                                         480
catececege egagagetae acettettea ttgacatect getegacact ateagggatg
                                                                        540
aaaatcgcng ggttgctcca gaaaggctnc aanaanatcc ttttcnctga aggccccgg
                                                                        600
athenetagt netagaateg geoegecate geggtggane etceaacett tegttneeet
                                                                        660
ttactgaggg ttnattgccg cccttggcgt tatcatggtc acnccngttn cctqtgttga
                                                                        720
aattnttaac ccccacaat tccacgccna cattng
                                                                        756
      <210> 35
      <211> 834
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(834)
      <223> n = A, T, C or G
      <400> 35
ggggatetet anatenacet gnatgeatgg ttgteggtgt ggtegetgte gatgaanatg
                                                                         60
aacaggatet tgcccttgaa getetegget getgtnttta agttgctcag tetgeegtea
                                                                        120
tagtcagaca cnctcttggg caaaaaacan caggatntga gtcttgattt cacctccaat
                                                                        180
aatettengg getgtetget eggtgaacte gatgaenang ggeagetggt tgtgtntgat
                                                                        240
aaantccanc angtteteet tggtgacete eeetteaaag ttgtteegge etteateaaa
                                                                        300
cttctnnaan angannance canctttgte gagetggnat ttgganaaca eqteactgtt
                                                                        360
ggaaactgat cccaaatggt atgtcatcca tcgcctctgc tgcctgcaaa aaacttgctt
                                                                        420
ggcncaaatc cgactccccn tccttgaaag aagccnatca caccccctc cctggactcc
                                                                        480
nncaangact ctnccgctnc cccntccnng cagggttggt ggcannccgg gcccntgcgc
                                                                        540
ttcttcagcc agttcacnat nttcatcagc ccctctgcca gctgttntat tccttggggg
                                                                        600
ggaanccgtc tctcccttcc tgaannaact ttgaccgtng gaatagccgc gcntcnccnt
                                                                        660
achtnotggg cogggttcaa anteceteen ttgnennten cetegggeca ttetggattt
                                                                        720
nccnaacttt ttccttcccc cnccccncgg ngtttggntt tttcatnggg ccccaactct
                                                                        780
getnttggcc anteccetgg gggcntntan enceceetnt ggtccentng ggcc
                                                                        834
      <210> 36
      <211> 814
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(814)
      <223> n = A, T, C or G
      <400> 36
```

cggncgcttt ccngccgcgc cccgtttcca	tgacnaaggc	tcccttcang	ttaaatacnn	60
cctagnaaac attaatgggt tgctctacta	atacatcata	cnaaccagta	agcctgccca	120
naacgccaac tcaggccatt cctaccaaag	gaagaaaggc	taatetetee	accccctgta	180
ggaaaggcct gccttgtaag acaccacaat	neggetgaat	ctnaactett	atattttact	240
aatggaaaaa aaaaataaac aanaggtttt	gttctcatgg	ctgcccaccg	cageetggea	300
ctaaaacanc ccagcgctca cttctgcttg	ganaaatatt	ctttgctctt	ttggacatca	360
ggcttgatgg tatcactgcc acntttccac				420
antganctgg aaggcctgaa ncttagtctc				480
				540
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aagaagataa tatattocaa goanatacaa aatatotaat gaaagatoaa ggoaggaaaa
                                                                           180
tgantataac taattgacaa tggaaaatca attttaatgt gaattgcaca ttatccttta
                                                                           240
aaagctttca aaanaaanaa ttattgcagt ctanttaatt caaacagtgt taaatggtat
                                                                           300
caggataaan aactgaaggg canaaagaat taattttcac ttcatgtaac ncacccanat
                                                                           360
ttacaatggc ttaaatgcan ggaaaaagca gtggaagtag ggaagtantc aaggtctttc
                                                                           420
tggtctctaa tctgccttac tctttgggtg tggctttgat cctctggaga cagctgccag
                                                                           480
ggctcctgtt atatccacaa tcccagcagc aagatgaagg gatgaaaaag gacacatgct
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gccttccttt gaggagactt catctcactg gccaacactc agtcacatgt
                                                                           590
       <210> 47
       <211> 774
       <212> DNA
       <213> Homo sapien
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       <223> n = A, T, C or G
      <400> 47
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tgaacagaat tttcctgnac aacggggctt caaaataatt ttcttgggga ggttcaagac
                                                                          120
gcttcactgc ttgaaactta aatggatgtg ggacanaatt ttctgtaatg accctgaggg
                                                                          180
cattacagac gggactctgg gaggaaggat aaacagaaag gggacaaagg ctaatcccaa
                                                                          240
aacatcaaag aaaggaaggt ggcgtcatac ctcccagcct acacagttct ccagggctct
                                                                          300
cctcatccct ggaggacgac agtggaggaa caactgacca tgtccccagg ctcctgtgtg
                                                                          360
ctggctcctg gtcttcagcc cccagctctg gaagcccacc ctctgctgat cctgcgtggc
                                                                          420
ccacactect tqaacacaca tecceaggtt atatteetgg acatggetga acctectatt
                                                                          480
cetactteeg agatgeettg etceetgeag cetgteaaaa teccacteae cetecaaace
                                                                          540
acggcatggg aagcctttct gacttgcctg attactccag catcttqqaa caatccctqa
                                                                          600
ttccccactc cttagaggca agatagggtg gttaagagta gggctggacc acttggagcc aggctgctgg cttcaaattn tggctcattt acgagctatg ggaccttggg caagtnatct
                                                                          660
                                                                          720
tcacttctat gggcntcatt ttgttctacc tgcaaaatgg gggataataa tagt
                                                                          774
      <210> 48
      <211> 124
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (124)
      <223> n = A, T, C or G
      <400> 48
canaaattga aattttataa aaaggcattt ttctcttata tccataaaat gatataattt
                                                                           60
ttgcaantat anaaatgtgt cataaattat aatgttcctt aattacagct caacgcaact
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```

<212> DNA <213> Homo sapien

tggt				124
<210> 49 <211> 147 <212> DNA				
<213> Homo sapien			100.7	
<220>			tan e e e	
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<223> n = A, T, C  or  G				
<400> 49				
gccgatgcta ctattttatt gcaggaggtg	ggggtgtttt	tattattctc	tcaacagctt	60
tgtggctaca ggtggtgtct gactgcatna	aaaantttt	tacgggtgat	tgcaaaaatt	120 147
ttagggcacc catateccaa gcantgt				14/
<210> 50	•			
<211> 107			•	
<212> DNA				
<213> Homo sapien				
<400> 50				
acattaaatt aataaaagga ctgttggggt	tctgctaaaa	cacatggctt	gatatattgc	60
atggtttgag gttaggagga gttaggcata	tgttttggga	gaggggt		107
<210> 51				
<211> 204				
<212> DNA				
<213> Homo sapien				
4400 F1				
<pre>&lt;400&gt; 51 gtcctaggaa gtctagggga cacacgactc</pre>	tagaatcaca	adaccascsc	acttacacaa	60
cgggaaggaa aggcagagaa gtgacaccgt				120
gccttgcaag gtcagaaagg ggactcaggg				180
cctccctttt gggaccagca atgt				204
<210> 52				
<211> 491				
<212> DNA				
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<220> <221> misc feature				
<221> MISC_leature <222> (1)(491)				
$\langle 223 \rangle$ n = A,T,C or G		٠	•	
		•		× *
<400> 52				<b>CO</b>
acaaagataa catttatctt ataacaaaaa qqqtattttc caaaaqacta aagagataac				60 120
ccatcaqaca ggtttttaaa aaacaacata				180
aaaacttctt gtatcaattt cttttgttca				240
tcanaaacac ttcctcaaaa attttcaana	tggtagcttt	canatgtncc	ctcagtccca	300
atgttgctca gataaataaa tctcgtgaga	acttaccacc	caccacaagc	tttctggggc	360
atgcaacagt gtctttctt tncttttct				420
caattttatt tggataacaa agggtctcca	aattatattg	aaaaataaat	ccaagttaat	480
atcactcttg t				491
<210> 53				
<211> 484				

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<220>
       <221> misc_feature
       <222> (1) ... (484)
       <223> n = A, T, C or G
       <400> 53
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gtattaacag ttgctgaagt ttggtatttt tatgcagcat tttctttttg ctttgataac
                                                                         120
actacagaac ccttaaggac actgaaaatt agtaagtaaa gttcagaaac attagctgct
                                                                        180
caatcaaatc tctacataac actatagtaa ttaaaacgtt aaaaaaaagt qttqaaatct
                                                                         240
gcactagtat anaccgctcc tgtcaggata anactgcttt ggaacagaaa gggaaaaanc
                                                                         300
agetttgant ttetttgtge tgatangagg aaaggetgaa ttacettgtt geeteteeet
                                                                        360
aatgattggc aggtcnggta aatnccaaaa catattccaa ctcaacactt cttttccncg
                                                                        420
tancttgant ctgtgtattc caggancagg cggatggaat gggccagccc ncggatgttc
                                                                        480
                                                                        484
      <210> 54
      <211> 151
      <212> DNA
      <213> Homo sapien
      <400> 54
actaaacctc gtgcttgtga actccataca gaaaacggtg ccatccctga acacggctgg
                                                                         60
ccactgggta tactgctgac aaccgcaaca acaaaaacac aaatccttgg cactggctag
                                                                        120
tctatgtcct ctcaagtgcc tttttgtttg t
                                                                        151
      <210> 55
      <211> 91
      <212> DNA
      <213> Homo sapien
      <400> 55
acctggcttg tctccgggtg gttcccggcg cccccacgg tccccagaac ggacactttc
                                                                         60
gccctccagt ggatactcga gccaaagtgg t
                                                                         91
      <210> 56
      <211> 133
      <212> DNA
      <213> Homo sapien
      <400> 56
ggcggatgtg cgttggttat atacaaatat gtcattttat gtaagggact tgagtatact
                                                                         60
tggatttttg gtatctgtgg gttgggggga cggtccagga accaataccc catggatacc
                                                                        120
aagggacaac tgt
                                                                        133
      <210> 57
      <211> 147
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(147)
      <223> n = A, T, C or G
      <400> 57
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                                                                         60
gactgggagc tgagcccttc cctttgcgcc tgcctcagag gattgttgcc gacntgcana
                                                                        120
tctcantggg ctggatncat gcagggt
                                                                        147
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<210> 58

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<211> 198
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
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       <223> n = A, T, C or G
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 tgattacata catttatcct ttaaaaaaga tgtaaatctt aatttttatg ccatctatta
                                                                         120
 atttaccaat gagttacctt gtaaatgaga agtcatgata gcactgaatt ttaactagtt
                                                                         180
                                                                         198
 ttgacttcta agtttggt
       <210> 59
       <211> 330
       <212> DNA
       <213> Homo sapien
       <400> 59
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                                                                          60
 ccattgaaaa ttatcattaa tgattttaaa tgacaagtta tcaaaaactc actcaatttt
                                                                         120
                                                                         180
 cacctgtgct agcttgctaa aatgggagtt aactctagag caaatatagt atcttctgaa
 tacagtcaat aaatgacaaa gccagggcct acaggtggtt tccagacttt ccagacccag
                                                                         240
                                                                         300
 caqaaqqaat ctattttatc acatggatct ccgtctgtgc tcaaaatacc taatgatatt
                                                                         330
. tttcqtcttt attqqacttc tttqaaqagt
       <210> 60
       <211> 175
       <212> DNA
       <213> Homo sapien
       <400> 60
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                                                                          60
 qteqtqqct cetteetett catecteate cagetggtge tgeteatega etttgegeae
                                                                         120
                                                                         175
 tectggaace ageggtgget gggcaaggee gaggagtgeg attecegtge etggt
       <210> 61
       <211> 154
       <212> DNA
       <213> Homo sapien
       <400> 61
 accecacttt teeteetgtg ageagtetgg actteteact getacatgat gagggtgagt
                                                                          60
 ggttgttgct cttcaacagt atcctcccct ttccggatct gctgagccgg acagcagtgc
                                                                         120
                                                                         154
 tggactgcac agccccgggg ctccacattg ctgt
       <210> 62
       <211> 30
       <212> DNA
       <213> Homo sapien
       <400> 62
                                                                          30
 cgctcgagcc ctatagtgag tcgtattaga
       <210> 63
       <211> 89
       <212> DNA
       <213> Homo sapien
       <400> 63
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ctgtatgaat aaaaatggtt a		aaactgacca	tcttttatat	ttaatgcttc	60 89
					•
<210> 64 <211> 97					
<211> 37 <212> DNA					
<213> Homo sapien					
•					
<400> 64					
accggagtaa ctgagtcggg ac			aataaataaa	ggttctgcag	60
aatcagtgca tccaggattg gt	tccttggat	ctggggt			97
<210> 65					
<211> 377					
<212> DNA				•	
<213> Homo sapien					
<220>					
<221> misc_feature			· .		
<222> (1) (377)	•				
<223> n = A, T, C or	r G				
<400> 65					
acaacaanaa ntcccttctt ta	aggccactg	atggaaacct	ggaaccccct	tttgatggca	60
gcatggcgtc ctaggccttg acccaacctgg tctacccaca nt	tetaaeta	tagactatet	ctoccactoa	accgcacacc	120 180
tcggtcataa natgaaatcc ca					240
ggtgctgttt gctcagccag aa	aacagctg	cctggcattc	gccgctgaac	tatgaacccg	300
tgggggtgaa ctacccccan ga	ggaatcat	gcctgggcga	tgcaanggtg	ccaacaggag	360
gggcgggagg agcatgt			4 4		377
<210> 66					
<210> 00 <211> 305					
<212> DNA					
<213> Homo sapien			* *	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	
<400> 66			eri Andria Andria de la composición de la c	ara wasan wasan in	<b>C</b> 0
acgeetttee eteagaatte ag agaaccegtg tgeeeettee ca	ggaagaga	acceteacte	catctttcaa	ctorrace	60 120
aggaactaac tgcaccctgg tc					180
toctocacto taagggatat ca	acactgcc	cagcacaggg	gccctgaatt	tatgtggttt	240
ttatatattt tttaataaga tg	cactttat	gtcattttt	aataaagtct	gaagaattac	300
tgttt				1 .	305
<210> 67					
<210> 67 <211> 385		-	-	24 E	
<212> DNA				•	
<213> Homo sapien					
_				,	
<400> 67				*	
actacacaca ctccacttgc cc	ttgtgaga	cactttgtcc	cagcacttta	ggaatgctga	60
ggtcggacca gccacatctc at cccttttaaa aaaggggact tg	gigcaaga cttaaaaa	agaagtetag	ccaccattat	ctgagagttc	120 180
tgtgctgtgc tggagattca ct	tttgagag	agttctcctc	tgagacctga	tctttagagg	240
ctgggcagtc ttgcacatga ga	tggggctg	gtctgatctc	agcactcctt	agtctgcttg	300
ecteteceag ggeeceagee tg	gccacacc	tgcttacagg	gcactctcag	atgcccatac	360
catagtttct gtgctagtgg ac	cgt				385
<210> 68					
<210> 66 <211> 73					
<211> /3 <212> DNA					
<213> Homo sapien					

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<400> 68
acttaaccag atatattttt accccagatg gggatattct ttgtaaaaaa tgaaaataaa
                                                                           60
gtttttttaa tgg
      <210> 69
      <211> 536
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(536)
      <223> n = A, T, C or G
      <400> 69
actagtccag tgtggtggaa ttccattgtg ttgggggctc tcaccctcct ctcctgcagc
                                                                          60
tocagettig tgetetgeet etgaggagae catggeecag catetgagta ecetgetget
                                                                         120
cctgctggcc accctagctg tggccctggc ctggagccc aaggaggagg ataggataat
                                                                         180
cccgggtggc atctataacg cagacctcaa tgatgagtgg gtacagcgtg cccttcactt
                                                                         240
cgccatcagc gagtataaca aggccaccaa agatgactac tacagacgtc cgctgcgggt
                                                                         300
actaagagcc aggcaacaga ccgttggggg ggtgaattac ttcttcgacg tagaggtggg
                                                                         360
cegaaccata tgtaccaagt eccageccaa ettggacace tgtgeettee atgaacagee
                                                                         420
agaactgcag aagaaacagt tgtgctcttt cgagatctac gaagttccct ggggagaaca
                                                                         480
gaangtoot gggtgaaato caggtgtcaa gaaatootan ggatotgttg coaggo
                                                                         536
      <210> 70
      <211> 477
      <212> DNA
      <213> Homo sapien
     <400> 70
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teactteeac tecataacge tecteatact aggeetacta accaacacac taaccatata
                                                                         120
                                                                         180
ccaatgatgg cgcgatgtaa cacgagaaag cacataccaa ggccaccaca caccacctgt
ccaaaaaggc cttcgatacg ggataatcct atttattacc tcagaagttt ttttcttcgc agggattttt ctgagccttt taccactcca gcctagcccc taccccccaa ctaggagggc
                                                                         240
                                                                          300
actggcccc aacaggcatc accccgctaa atcccctaga agtcccactc ctaaacacat
                                                                         360
ccqtattact cqcatcagga gtatcaatca cctgagctca ccatagtcta atagaaaaca
                                                                         420
accgaaacca aattattcaa agcactgctt attacaattt tactgggtct ctatttt
                                                                         477
      <210> 71
      <211> 533
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (533)
      <223> n = A, T, C or G
      <400> 71
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                                                                          60
                                                                         120
aggtattaat agatatgtaa agaaagaaat cacaccatta ataatggtaa gattggttta
tgtgatttta gtggtatttt tggcaccctt atatatgttt tccaaacttt cagcagtgat
                                                                         180
attatttcca taacttaaaa agtgagtttg aaaaagaaaa tctccagcaa gcatctcatt
                                                                         240
                                                                         300
tagatagagg tttqtcatct ttagaaatac agcaatatqt gacttttaa aaaaqctqtc
                                                                         360
aaataqqtqt qaccctacta ataattatta gaaatacatt taaaaacatc gagtacctca
agtcagtttg ccttgaaaaa tatcaaatat aactcttaga gaaatgtaca taaaagaatg
                                                                         420
cttcgtaatt ttggagtang aggttccctc ctcaattttg tatttttaaa aagtacatgg
                                                                         480
taaaaaaaaa aattcacaac agtatataag gctgtaaaat gaagaattct gcc
                                                                         533
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<211> 511
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(511)
       <223> n = A, T, C or G
       <400> 72
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                                                                            60
 aaatgaaagg cttccaggca gttatctgat taaagaacac taaaagaggg acaaggctaa
                                                                          120
 aagccgcagg atgtctacac tatancaggc gctatttggg ttggctggag gagctgtgga
                                                                          180
 aaacatggan agattggtgc tgganategc cgtggctatt cctcattgtt attacanagt
                                                                           240
 gaggttetet gtgtgeecae tggtttgaaa accgttetne aataatgata gaatagtaca
                                                                           300
 cacatgagaa ctgaaatggc ccaaacccag aaagaaagcc caactagatc ctcaqaanac
                                                                          360
 gettetaggg acaataaccg atgaagaaaa gatggcetee ttgtgceece gtetgttatg
                                                                           420
 atttctctcc attgcagcna naaacccgtt cttctaagca aacncaggtg atgatggcna
                                                                           480
 aaatacaccc cctcttgaag naccnggagg a
                                                                          511
       <210> 73
       <211> 499
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(499)
       <223> n = A, T, C or G
       <400> 73
cagtgccagc actggtgcca gtaccagtac caataacagt gccagtgcca gtgccagcac
                                                                           60
cagtggtggc ttcagtgctg gtgccagcct gaccgccact ctcacatttg ggctcttcgc
                                                                          120
tggccttggt ggagctggtg ccagcaccag tggcagctct ggtgcctgtg gtttctccta caagtgagat tttagatatt gttaatcctg ccagtctttc tcttcaagcc agggtgcatc
                                                                          180
                                                                          240
ctcagaaacc tactcaacac agcactctag gcagccacta tcaatcaatt gaagttgaca
                                                                          300
360
antictagagg geocgittaa accegetgat cageetegae tgtgeettet antiqeeage
                                                                          420
catctgttgt ttgcccctcc cccgntgcct tccttgaccc tggaaagtgc cactcccact
                                                                          480
gtcctttcct aantaaaat
                                                                          499
      <210> 74
      <211> 537
       <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(537)
      <223> n = A, T, C or G
      <400> 74
tttcatagga gaacacactg aggagatact tgaagaattt ggattcagcc gcgaagagat
ttatcagctt aactcagata aaatcattga aagtaataag gtaaaagcta gtctctaact
                                                                          120 ·
tccaggccca cggctcaagt gaatttgaat actgcattta cagtgtagag taacacataa
                                                                          180
cattgtatgc atggaaacat ggaggaacag tattacagtg tcctaccact ctaatcaaga
                                                                          240
aaagaattac agactctgat tctacagtga tgattgaatt ctaaaaatgg taatcattag ggcttttgat ttataanact ttgggtactt atactaaatt atggtagtta tactgccttc
                                                                          300
                                                                          360
cantttactt gatatatttg ttgatattaa gattcttgac ttatattttg aatgggttct
                                                                          420
actgaaaaan gaatgatata ttcttgaaga catcgatata catttattta cactcttgat
                                                                          480
totacaatgt agaaaatgaa ggaaatgccc caaattgtat ggtgataaaa gtcccqt
                                                                          537
```

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<210> 75
      <211> 467
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(467)
      <223> n = A, T, C or G
      <400> 75
caaanacaat tgttcaaaag atgcaaatga tacactactg ctgcagctca caaacacctc
                                                                        60
tgcatattac acgtacctcc tcctgctcct caagtagtgt ggtctatttt gccatcatca
                                                                       120
cctgctgtct gcttagaaga acggctttct gctgcaangg agagaaatca taacagacgg
                                                                       180
tggcacaagg aggccatctt ttcctcatcg gttattgtcc ctagaagcgt cttctgagga
                                                                       240
tctagttggg ctttctttct gggtttgggc catttcantt ctcatgtgtg tactattcta
                                                                       300
tcattattqt ataacqqttt tcaaaccngt gggcacncag agaacctcac tctgtaataa
                                                                       360
caatgaggaa tagccacggt gatctccagc accaaatctc tccatgttnt tccagagctc
                                                                       420
ctccagccaa cccaaatagc cgctgctatn gtgtagaaca tccctgn
                                                                       467
      <210> 76
      <211> 400
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (400)
      <223> n = A, T, C or G
      <400> 76
aagetgacag cattegggee gagatgtete geteegtgge ettagetgtg etegegetae
                                                                        60
tetetette tggeetggag getatecage gtactecaaa gatteaggtt tacteaegte
                                                                       120
atccagcaga gaatggaaag tcaaatttcc tgaattgcta tgtgtctggg tttcatccat
                                                                       180
ccgacattga agttgactta ctgaagaatg gagagagaat tgaaaaagtg gagcattcag
                                                                       240
acttgtettt cagcaaggae tggtetttet atetettgta etacactgaa tteacececa
                                                                       300
ctgaaaaaga tgagtatgcc tgccgtgtga accatgtgac tttgtcacag cccaagatng
                                                                       360
ttnagtggga tcganacatg taagcagcan catgggaggt
                                                                       400
      <210> 77
      <211> 248
      <212> DNA
      <213> Homo sapien
      <400> 77
ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct
                                                                        60
ccagetgeec eggegggga tgegaggete ggageacect tgeeeggetg tgattgetge
                                                                       120
cagging teateteage tittetgice ettigetece ggcaageget tetgetgaaa
                                                                       180
gttcatatct ggagcctgat gtcttaacga ataaaggtcc catgctccac ccgaaaaaaa
                                                                       240
aaaaaaa
                                                                       248
      <210> 78
      <211> 201
      <212> DNA
      <213> Homo sapien
      <400> 78
actagtccag tgtggtggaa ttccattgtg ttgggcccaa cacaatggct acctttaaca
                                                                        60
                                                                       120
teacecaque ecegecetge eegtgeecea egetgetget aacgaeagta tgatgettae
totgotacto ggaaactatt tttatgtaat taatgtatgo tttottgttt ataaatgoot
                                                                       180
                                                                       201
gatttaaaaa aaaaaaaaa a
```

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<210> 79
       <211> 552
       <212> DNA
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       <220>
       <221> misc_feature
       <222> (1)...(552)
       <223> n = A, T, C or G
       <400> 79
tccttttgtt aggtttttga gacaacccta gacctaaact gtgtcacaga cttctgaatg
                                                                         60
tttaggcagt gctagtaatt teetegtaat gattetitta ttaettteet attetttatt
                                                                        120
cctctttctt ctgaagatta atgaagttga aaattgaggt ggataaatac aaaaaggtag
                                                                        180
tgtgatagta taagtatcta agtgcagatg aaagtgtgtt atatatatcc attcaaaatt
                                                                        240
atgcaagtta gtaattactc agggttaact aaattacttt aatatgctgt tgaacctact
                                                                        300
ctgttccttg gctagaaaaa attataaaca ggactttgtt agtttgggaa gccaaattga
                                                                        360
taatattota tgttotaaaa gttgggotat acataaanta tnaagaaata tggaatttta
                                                                        420
ttcccaggaa tatggggttc atttatgaat antacccggg anagaagttt tgantnaaac
                                                                        480
cngttttggt taatacgtta atatgtcctn aatnaacaag gcntgactta tttccaaaaa
                                                                        540
aaaaaaaaa aa
                                                                        552
      <210> 80
      <211> 476
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(476)
      <223> n = A, T, C or G
      <400> 80
acagggattt gagatgctaa ggccccagag atcgtttgat ccaaccctct tattttcaga
ggggaaaatg gggcctagaa gttacagagc atctagctgg tgcgctggca cccctggcct
                                                                        120
cacacagact cocgagtage tgggactaca ggcacacagt cactgaagca ggccctgttt
                                                                        180
geaatteacg ttgccacctc caacttaaac attetteata tgtgatgtcc ttagtcacta
                                                                        240
aggttaaact ttcccacca gaaaaggcaa cttagataaa atcttagagt actttcatac
                                                                        300
tottctaagt cotottccag cotcactttg agtoctcott gggggttgat aggaantntc
                                                                        360
tcttggcttt ctcaataaaa tctctatcca tctcatgttt aatttggtac gcntaaaaat
                                                                        420
gctgaaaaaa ttaaaatgtt ctggtttcnc tttaaaaaaa aaaaaaaaa aaaaaa
                                                                        476
      <210> 81
      <211> 232
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (232)
      <223> n = A, T, C or G
      <400> 81
ttttttttg tatgccntcn ctgtggngtt attgttgctg ccaccctgga ggagcccagt
                                                                        60
ttettetgta tetttettt etgggggate tteetggete tgeeceteca tteecageet
                                                                       120
ctcatcccca tcttgcactt ttgctagggt tggaggcgct ttcctggtag cccctcagag
                                                                       180
actcagtcag cgggaataag tcctaggggt ggggggtgtg gcaagccggc ct
                                                                       232
      <210> 82
      <211> 383
      <212> DNA
      <213> Homo sapien
```

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<220>
       <221> misc feature
        <222> (1)...(383)
       <223> n = A, T, C or G
       <400> 82
 aggegggage agaagetaaa geeaaageee aagaagagtg geagtgeeag caetggtgee
                                                                          60
 agtaccagta ccaataacat gccagtgcca gtgccagcac cagtggtggc ttcagtgctg
                                                                         120
 gtgccagcct gaccgccact ctcacatttg ggctcttcgc tggccttggt ggagctggtg
                                                                         180
 ccaqcaccaq tqqcaqctct qqtqcctqtq qtttctccta caagtgagat tttagatatt
                                                                         240
 gttaatcctg ccagtctttc tcttcaagcc agggtgcatc ctcagaaacc tactcaacac
                                                                         300
 agcactctng gcagccacta tcaatcaatt gaagttgaca ctctgcatta aatctatttg
                                                                         360
                                                                         383
 ccatttcaaa aaaaaaaaaa aaa
       <210> 83
       <211> 494
        <212> DNA
        <213> Homo sapien
       <220>
        <221> misc_feature
       <222> (1)...(494)
       <223> n = A, T, C or G
       <400> 83
. accgaattgg gaccgctggc ttataagcga tcatgtcctc cagtattacc tcaacgagca
                                                                          60
 gggagatcga gtctatacgc tgaagaaatt tgacccgatg ggacaacaga cctgctcagc
                                                                         120
                                                                         180
 ccatectget eggttetece cagatgacaa atactetega cacegaatea ecateaagaa
 acqcttcaaq qtqctcatqa cccaqcaacc gcgccctqtc ctctgagggt ccttaaactg
                                                                         240
 atgtetttte tgccacetgt tacccetegg agacteegta accaaactet teggactgtg
                                                                         300
 agecetqatq cetttttgcc agecatacte tttggentee agtetetegt ggegattgat
                                                                         360
                                                                         420
 tatgcttgtg tgaggcaatc atggtggcat cacccatnaa gggaacacat ttganttttt
 tttcncatat tttaaattac naccagaata nttcagaata aatgaattga aaaactctta
                                                                         480
                                                                         494
 aaaaaaaaa aaaa
       <210> 84
       <211> 380
        <212> DNA
        <213> Homo sapien
       <220>
       <221> misc_feature
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       <223> n = A, T, C or G
       <400> 84
 gctggtagcc tatggcgtgg ccacggangg gctcctgagg cacgggacag tgacttccca
                                                                          60
                                                                         120
 agtatectge geogegtett ctacegtece tacetgeaga tettegggea gatteeceag
 gaggacatgg acgtggccct catggagcac agcaactgct cgtcggagcc cggcttctgg
                                                                         180
 gcacaccete etggggeeea ggegggeace tgegteteee agtatgeeaa etggetggtg
                                                                         240
 gtgctgctcc tcgtcatctt cctgctcgtg gccaacatcc tgctggtcac ttgctcattg
                                                                         300
 ccatgttcag ttacacattc ggcaaagtac agggcaacag cnatctctac tgggaaggcc
                                                                         360
                                                                         380
 agcgttnccg cctcatccgg
       <210> 85
       <211> 481
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
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<222> (1)...(481)

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<223> n = A, T, C or G
       <400> 85
 gagttagete etecacaace ttgatgaggt egtetgeagt ggeetetege tteatacege
                                                                            60
 tnccatcgtc atactgtagg tttgccacca cctcctgcat cttggggcgg ctaatatcca
                                                                           120
 ggaaactete aatcaagtea cegtenatna aacetgtgge tggttetgte tteegetegg
                                                                           180
 tgtgaaagga tctccagaag gagtgctcga tcttccccac acttttgatg actttattga
                                                                           240
 gicgattetg catgiceage aggaggitgt accagetete tgacagigag gicaccagee
                                                                           300
 ctatcatgcc nttgaacgtg ccgaagaaca ccgagccttg tgtggggggt gnagtctcac
                                                                           360
 ccagattctg cattaccaga nagccgtggc aaaaganatt gacaactcgc ccaggnngaa
                                                                           420
 aaagaacace teetggaagt getngeeget eetegteent tggtggnnge gentneettt
                                                                           480
                                                                           481
       <210> 86
       <211> 472
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(472)
      <223> n = A, T, C or G
      <400> 86
aacatcttcc tgtataatgc tgtgtaatat cgatccgatn ttgtctgctg agaattcatt
                                                                            60
acttggaaaa gcaacttnaa gcctggacac tggtattaaa attcacaata tgcaacactt
                                                                           120
taaacagtgt gtcaatctgc tecettactt tgtcatcacc agtctgggaa taagggtatg
                                                                           180
ccctattcac acctgttaaa agggcgctaa gcatttttga ttcaacatct tttttttga cacaagtccg aaaaaagcaa aagtaaacag ttnttaattt gttagccaat tcacttctt
                                                                           240
                                                                          300
catgggacag agccatttga tttaaaaagc aaattgcata atattgagct ttgggagctg
                                                                           360
atatntgage ggaagantag cetteetact teaceagaca caacteettt catattggga
                                                                           420
tgttnacnaa agttatgtct cttacagatg ggatgctttt gtggcaattc tg
                                                                           472
      <210> 87
      <211> 413
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (413)
      <223> n = A, T, C or G
      <400> 87
agaaaccagt atctctnaaa acaacctctc ataccttgtg gacctaattt tgtgtgcgtg
                                                                           60
tgtgtgtgcg cgcatattat atagacaggc acatcttttt tacttttgta aaagcttatg
                                                                          120
cctctttggt atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct
                                                                          180
ttgtcttctg tgtaaatggt actagagaaa acacctatnt tatgagtcaa tctagttngt
                                                                          240
tttattcgac atgaaggaaa tttccagatn acaacactna caaactctcc cttgactagg
                                                                          300
ggggacaaag aaaagcanaa ctgaacatna gaaacaattn cctggtgaga aattncataa
                                                                          360
acagaaattg ggtngtatat tgaaananng catcattnaa acgtttttt ttt
                                                                          413
      <210> 88
      <211> 448
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(448)
      <223> n = A, T, C or G
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<400> 88
cgcagcgggt cctctctatc tagctccagc ctctcgcctg ccccactccc cgcgtcccgc
                                                                              60
gtoctageen accatggeeg ggeocetgeg egeceegetg etectgetgg ceatectgge
                                                                             120
cgtggccctg gccgtgagcc ccgcggccgg ctccagtccc ggcaagccgc cgcgcctggt
                                                                             180
gggaggccca tggaccccgc gtggaagaag aaggtgtgcg gcgtgcactg gactttgccg tcggcnanta caacaaaccc gcaacnactt ttaccnagcn cgcgctgcag gttgtgccgc
                                                                             240
                                                                             300
cccaancaaa ttgttactng gggtaantaa ttcttggaag ttgaacctgg gccaaacnng
                                                                             360
                                                                              420
tttaccagaa ccnagccaat tngaacaatt ncccctccat aacagcccct tttaaaaaagg
                                                                             448
quancantcc tgntcttttc caaatttt
      <210> 89
      <211> 463
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (463)
      <223> n = A, T, C or G
      <400> 89
                                                                               60
gaattttgtg cactggccac tgtgatggaa ccattgggcc aggatgcttt gagtttatca
gtagtgattc tgccaaagtt ggtgttgtaa catgagtatg taaaaatgtca aaaaattagc
                                                                             120
agaggtctag gtctgcatat cagcagacag tttgtccgtg tattttgtag ccttgaagtt
                                                                              180
                                                                              240
ctcaqtgaca agttnnttct gatgcgaagt tctnattcca gtgttttagt cctttgcatc
                                                                              300
tttnatgttn agacttgcct ctntnaaatt gcttttgtnt tctgcaggta ctatctgtgg
tttaacaaaa tagaannact tetetgettn gaanatttga atatettaca tetnaaaatn aattetetee ceatannaaa acceangeee ttggganaat ttgaaaaang gnteettenn
                                                                              360
                                                                              420
aattonnana anttoagntn toatacaaca naacnggano coc
                                                                              463
       <210> 90
       <211> 400
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(400)
       <223> n = A, T, C \text{ or } G
       <400> 90
agggattgaa ggtctnttnt actgtcggac tgttcancca ccaactctac aagttgctgt
                                                                               60
cttccactca ctgtctgtaa gcntnttaac ccagactgta tcttcataaa tagaacaaat
                                                                              120
tottcaccag toacatotto taggacottt ttggattcag ttagtataag ctottccact
                                                                              180
                                                                              240
tcctttgtta agacttcatc tggtaaagtc ttaagttttg tagaaaggaa tttaattgct
cgttctctaa caatgtcctc tccttgaagt atttggctga acaacccacc tnaagtccct
                                                                              300
                                                                              360
ttgtgcatcc attttaaata tacttaatag ggcattggtn cactaggtta aattctgcaa
                                                                              400
gagtcatctg tctgcaaaag ttgcgttagt atatctgcca
       <210> 91
       <211> 480
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(480)
       <223> n = A, T, C or G
       <400> 91
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gageteggat ceaataatet ttgtetgagg geageacaea tatneagtge eatggnaact

```
ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac
                                                                        120
atgestettt gastacegtg tgesagtget ggtgattets asacacetes nncegetett
                                                                        180
tgtggaaaaa ctggcacttg nctggaacta gcaagacatc acttacaaat tcacccacga
                                                                        240
gacacttgaa aggtgtaaca aagcgactct tgcattgctt tttgtccctc cggcaccagt
                                                                        300
tgtcaatact aaccegetgg tttgceteca teacatttgt gatetgtage tetggataca
                                                                        360
tctcctgaca gtactgaaga acttcttctt ttgtttcaaa agcaactctt ggtgcctgtt
                                                                        420
ngatcaggtt cccatttccc agtccgaatg ttcacatggc atatnttact tcccacaaaa
                                                                        480
       <210> 92
       <211> 477
       <212> DNA
       <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (477)
      <223> n = A, T, C or G
      <400> 92
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                                                                         60
ggtcccgctg tagccccagc gactctccac ctgctggaag cggttgatgc tgcactcctt
                                                                        120
cccacgcagg cagcagcggg gccggtcaat gaactccact cgtggcttgg ggttgacggt
                                                                        180
taantgcagg aagaggctga ccacctcgcg gtccaccagg atgcccgact gtgcgggacc
                                                                        240
tgcagcgaaa ctcctcgatg gtcatgagcg ggaagcgaat gangcccagg gccttgccca
                                                                        300
gaacetteeg cetgttetet ggegteacet geagetgetg eegetnacae teggeetegg
                                                                        360
accageggae aaaeggegtt gaacageege accteaegga tgeecantgt gtegegetee
                                                                        420
aggaacggen ccagcgtgtc caggtcaatg tcggtgaanc ctccgcgggt aatggcg
                                                                        477
      <210> 93
      <211> 377
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
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      <400> 93
gaacggctgg accttgcctc gcattgtgct gctggcagga ataccttggc aagcagctcc
agtocgagea geoccagace getgeegeee gaagetaage etgeetetgg cetteceete
                                                                        120
cgcctcaatg cagaaccant agtgggagca ctgtgtttag agttaagagt gaacactgtn
                                                                        180
tgattttact tgggaatttc ctctgttata tagcttttcc caatgctaat ttccaaacaa
                                                                        240
caacaacaaa ataacatgtt tgcctgttna gttgtataaa agtangtgat tctgtatnta
                                                                        300
aagaaaatat tactgttaca tatactgctt gcaanttctg tatttattgg tnctctggaa
                                                                        360
ataaatatat tattaaa
                                                                        377
      <210> 94
      <211> 495
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(495)
      <223> n = A, T, C or G
      <400> 94
ccctttgagg ggttagggtc cagttcccag tggaagaaac aggccaggag aantgcgtgc
                                                                        60
egagetgang cagattteee acagtgacee cagageeetg ggetatagte tetgaceeet
                                                                       120
ccaaggaaag accacettet ggggacatgg getggaggge aggacetaga ggcaccaagg
                                                                       180
gaaggcccca ttccggggct gttccccgag gaggaaggga aggggctctg tgtgccccc
                                                                       240
```

acgaggaana ggccctgant cctgggatca tgcaagctca ccaaggtccc ctctcagtcc acacccaccc agancancca cccgccatgg tggactctng tcccnnaagg gggcagaatc aaaaaaaana aaaaa	cttccctaca ggaatgtnct	ccctgaacgg caaggaatcg	ncactggccc cngggcaacg	300 360 420 480 495
<210> 95 <211> 472 <212> DNA <213> Homo sapien				
<220> <221> misc_feature <222> (1)(472) <223> n = A,T,C or G				
<pre>&lt;400&gt; 95 ggttacttgg tttcattgcc accacttagt cctctggaag ccttgcgcag agcggacttt tagctgtttt gagttgattc gcaccactgc tattattat cttgtgaaaa gtatacaatg atgatgaaaa gcaatagata tatattcttt atcggcaaaa tgtggagtgt atgttctttt ttggttattt tattgtaaat gaattacaaa tttanttcan taatttcttt ccttgtttac</pre>	gtaattgttg accacaactc aaaattttgt tattatgttn cacagtaata attcttaatt	gagaataact aatatgaaaa tcatactgta aattatgatt tatgcctttt taagaaaatg	gctgaatttt ctattnact tttatcaagt gccattatta gtaacttcac gtangttata	60 120 180 240 300 360 420 472
<210> 96 <211> 476 <212> DNA <213> Homo sapien				
<220> <221> misc_feature <222> (1)(476) <223> n = A,T,C or G				
<pre>&lt;400&gt; 96 ctgaagcatt tcttcaaact tntctacttt gtggtgaaat ttcaaaatta tatgtaactt ttttaactca tgatttttac acacacaatc attcttcaca gtagatgatg aaagagtcct agctggatac atacngtggg agttctataa tgtgttagtc tcaattccta ccacactgag gcaggtactc ctccagaaaa acngacaggg tacaaagtct atcttcctca nangtctgtn</pre>	ctactagttt cagaacttat ccagtgtctt actcatacct ggagcctccc caggcttgca	tactttctcc tatatagcct gngcanaatg cagtgggact aaatcactat tgaaaaagtn	cccaagtctt ctaagtcttt ttctagntat naaccaaaat attcttatct acatctgcgt	60 120 180 240 300 360 420 476
<210> 97 <211> 479 <212> DNA <213> Homo sapien		• .	· ·	
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<pre>&lt;400&gt; 97 actctttcta atgctgatat gatcttgagt aaataatgct gcaaacttaa tgttcttatg caatcgcaaa tcaaaactca caagtgctca gattgtgctc cttcggatat gattgtttct caggctacta gaattctgtt attggatatn</pre>	caaaatggaa tctgttgtag canatcttgg	cgctaatgaa atttagtgta gcaatnttcc	acacagetta ataagaetta ttagteaaat	60 120 180 240 300

gtgattatna aattaatca ntnnttttta natcaaagt ttcnatctta tttttccc	a ttttgtgttt	ggaantgtnn	aaatgaaatc	tgaatgtggg	360 420 479
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tcaactccag ctggattat	t ttggagcctg	caaatctatt	cctacttqta	cggactttga	180
agtgattcag tttcctcta	c ggatgagaga	ctggctcaag	aatatcctca	tgcagcttta	240
tgaagccact ctgaacacg	c tggttatcta	gatgagaaca	gagaaataaa	gtcagaaaat	300
ttacctggag aaaagaggc					360
ttaagaaaaa ctaccacat tttggaataa tcttgacgc				ctgaccaccc	420 461
<210> 99		N			
<211> 171	Annual Control				87 × 42
<212> DNA				. • .	
<213> Homo sap	ıen				
<400> 99		1	1 - 1 1 1		
gtggccgcgc gcaggtgtt					60
cggcgcctct gcgggcccg	a ggaggagcgg	ctggcgggtg	gggggagtgt	gacccaccct	120
cggtgagaaa agccttctc	t agcgatctga	gaggcgtgcc	ttgggggtac	C	171
<210> 100					
<211> 269					
<212> DNA <213> Homo sap:	i an				
vzisz nomo sap.	ren		and the second		
<400> 100		y 1	n na heart an		
cggccgcaag tgcaactcc					60
cgactgcgac gacggcggc					120
aaggetgage tgaegeegea cageeggaae agageeeggt	a gaggtegtgt Taaaccadaa	acctegagga	gaccttgacg	ccgtcgggga	180 240
cgagagatac gcaggtgcag		geeregggg	geeeeeggg	aayyycyycc	269
to a company of the state of	44.1				100
<210> 101			a e dia a		1 1 1 K 4 1 1
<211> 405 <212> DNA					
<213> Homo sapi	en				
<400> 101			6.5		
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gctagcaagg taacagggta ttgattggtt tgtctttatg	. gggcacggct	acatyticag	aaacdaadct	aataacatoo	120 180
agtgggtgca ccctccctgt	agaacctggt	tacaaagctt	qqqqcaqttc	acctggtctg	240
tgaccgtcat tttcttgaca	tcaatgttat	tagaagtcag	gatatctttt	agagagtcca	300
ctgttctgga gggagattag				gaaaaagttg	360
gatgatcagt acgaataccg	aggcatattc	tcatatcggt	ggcca		405
<210> 102			•		
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-					
<400> 102					
ttttttttt tttttttt	tttttttt	ttttttttt	tttttttt	ttttttttt	60

aggacttaat	ccatttttat	ttcaaaatgt	ctacaaattt	aatcccatta	tacggtattt	120
toasastota	aattattcaa	attagccaaa	teettaccaa	ataataccca	aaaatcaaaa	180
atatacttct	ttcaccaaac	ttgttacata	aattaaaaaa	atatatacoo	ctagtattt	240
casactacaa	ttatcttaac	actgcaaaca	ttttaaggaa	ctaaaataaa	aaaaaacact	300
caaageacaa	taaagggaac	aacaaattct	tttacaacac	cattataaaa	atcatatctc	360
asstattagg	ggaatatata	cttcacacgg	gatettaact	tttactcact	ttotttattt	420
ttttaaacca	ttatttaaaa	ccaacacaat	gaeetcaacc	ctggactagt	ccgcccacc	470
LLLLaaacca	ccgcccgggc	CCaacacaac	ggaarccccc	ccggaccagc		
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<2112						
	DNA					•
<b>\213</b> /	Homo sapie	311				
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120 Leu Leu Val Ala Asn Ile Leu Leu Val Asn Leu Leu Ile Ala Met Phe 140 135 Ser Tyr Thr Phe Gly Lys Val Gln Gly Asn Ser Asp Leu Tyr Trp Lys 150 155 Ala Gln Arg Tyr Arg Leu Ile Arg Glu Phe His Ser Arg Pro Ala Leu 165 170 Ala Pro Pro Phe Ile Val Ile Ser His Leu Arg Leu Leu Arg Gln 185 180 Leu Cys Arg Arg Pro Arg Ser Pro Gln Pro Ser Ser Pro Ala Leu Glu-200 His Phe Arg Val Tyr Leu Ser Lys Glu Ala Glu Arg Lys Leu Leu Thr 220 215 Trp Glu Ser Val His Lys Glu Asn Phe Leu Leu Ala Arg Ala Arg Asp 230 Lys Arg Glu Ser Asp Ser Glu Arg Leu Lys Arg Thr Ser Gln Lys Val 250 Asp Leu Ala Leu Lys Gln Leu Gly His Ile Arg Glu Tyr Glu Gln Arg 265 260 Leu Lys Val Leu Glu Arg Glu Val Gln Gln Cys Ser Arg Val Leu Gly 280 275 Trp Val Ala Glu Ala Leu Ser Arg Ser Ala Leu Leu Pro Pro Gly Gly 295 Pro Pro Pro Pro Asp Leu Pro Gly Ser Lys Asp 310

<210> 113 <211> 553

<212> PRT

<213> Homo sapien

<400> 113 Met Val Gln Arg Leu Trp Val Ser Arg Leu Leu Arg His Arg Lys Ala 10 Gln Leu Leu Val Asn Leu Leu Thr Phe Gly Leu Glu Val Cys Leu 25 20 Ala Ala Gly Ile Thr Tyr Val Pro Pro Leu Leu Glu Val Gly Val Glu Glu Lys Phe Met Thr Met Val Leu Gly Ile Gly Pro Val Leu Gly 55 Leu Val Cys Val Pro Leu Leu Gly Ser Ala Ser Asp His Trp Arg Gly 70 Arg Tyr Gly Arg Arg Pro Phe Ile Trp Ala Leu Ser Leu Gly Ile Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala Gly Trp Leu Ala Gly Leu 100 105 Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu Ala Leu Leu Ile Leu Gly 120 125 Val Gly Leu Leu Asp Phe Cys Gly Gln Val Cys Phe Thr Pro Leu Glu 140 135 Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg Gln Ala 155 150 Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu Gly Gly Cys Leu Gly Tyr 170 175 Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser Ala Leu Ala Pro Tyr Leu 185 190 Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu Leu Thr Leu Ile Phe Leu 200 195 Thr Cys Val Ala Ala Thr Leu Leu Val Ala Glu Glu Ala Ala Leu Gly 215 220 Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala Pro Ser Leu Ser Pro His

Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe Arg Asn Leu Gly Ala Leu 245 Leu Pro Arg Leu His Gln Leu Cys Cys Arg Met Pro Arg Thr Leu Arg 265 270 Arg Leu Phe Val Ala Glu Leu Cys Ser Trp Met Ala Leu Met Thr Phe 280 285 Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu Gly Leu Tyr Gln Gly Val 295 300 Pro Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp Glu Gly 315 310 Val Arg Met Gly Ser Leu Gly Leu Phe Leu Gln Cys Ala Ile Ser Leu 325 330 Val Phe Ser Leu Val Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg 345 340 Ala Val Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala 355 360 365 Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu 375 Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr Leu Ala 390 395 Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro Lys Tyr Arg Gly 405 410 Asp Thr Gly Gly Ala Ser Ser Glu Asp Ser Leu Met Thr Ser Phe Leu 420 425 430 Pro Gly Pro Lys Pro Gly Ala Pro Phe Pro Asn Gly His Val Gly Ala Gly Gly Ser Gly Leu Leu Pro Pro Pro Pro Ala Leu Cys Gly Ala Ser 460 455 Ala Cys Asp Val Ser Val Arg Val Val Gly Glu Pro Thr Glu Ala 475 470 Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile Leu Asp 485 490 Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met Gly Ser 505 510 500 Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met Val Ser Ala Ala 520 525 Gly Leu Gly Leu Val Ala Ile Tyr Phe Ala Thr Gln Val Val Phe Asp 535 Lys Ser Asp Leu Ala Lys Tyr Ser Ala 550

<210> 114

<211> 241

<212> PRT

<213> Homo sapien

<400> 114

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115
                             120
 Asp Tyr Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met
     130
                         135
                                            140
 Lys Gly Leu Lys Cys Cys Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp
                     150
                                        155
 Ser Pro Tyr Phe Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn
                 165
                                    170
 Asp Asn Val Thr Asn Thr Ala Asn Glu Thr Cys Thr Lys Gln Lys Ala
                                185
 His Asp Gln Lys Val Glu Gly Cys Phe Asn Gln Leu Leu Tyr Asp Tle
                            200
 Arg Thr Asn Ala Val Thr Val Gly Gly Val Ala Ala Gly Ile Gly Gly
                        215
                                            220
 Leu Glu Leu Ala Ala Met Ile Val Ser Met Tyr Leu Tyr Cys Asn Leu
 225
                    230
                                        235
 Gln
      <210> 115
       <211> 366
      <212> DNA
       <213> Homo sapien
      <400> 115
getettete tecceteete tgaatttaat tettteaact tgeaatttge aaggattaca
                                                                      60
120
ttggtttgtg aatccatctt gctttttccc cattggaact agtcattaac ccatctctga
                                                                      180
actggtagaa aaacatctga agagctagtc tatcagcatc tgacaggtga attggatggt
                                                                      240
teteagaace attteaceca gacageetgt ttetateetg tttaataaat tagtttgggt
                                                                      300
tetetacatg cataacaaac cetgetecaa tetgteacat aaaagtetgt gaettgaagt
                                                                      360
ttagtc
                                                                      366
      <210> 116
      <211> 282
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(282)
      <223> n = A, T, C or G
      <400> 116
acaaagatga accattteet atattatage aaaattaaaa tetaceegta ttetaatatt
                                                                      60
gagaaatgag atnaaacaca atnttataaa gtctacttag agaagatcaa gtgacctcaa
                                                                     120
agactttact attttcatat tttaagacac atgatttatc ctattttagt aacctggttc
                                                                     180
atacgttaaa caaaggataa tgtgaacagc agagaggatt tgttggcaga aaatctatgt
                                                                     240
tcaatcinga actatciana tcacagacat tictaticci ti
                                                                     282
      <210> 117
      <211> 305
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(305)
      <223> n = A, T, C or G
      <400> 117
acacatgtcg cttcactgcc ttcttagatg cttctggtca acatanagga acagggacca
                                                                      60
tatttatcct ccctcctgaa acaattgcaa aataanacaa aatatatgaa acaattgcaa
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aataaggcaa aatatatgaa acaacaggtc tcgagatatt ggaaatcagt caatgaagga
                                                                          180
tactgatccc tgatcactgt cctaatgcag gatgtgggaa acagatgagg tcacctctgt
                                                                          240
                                                                          300
gactgcccca gcttactgcc tgtagagagt ttctangctg cagttcagac agggagaaat
                                                                          305
tgggt
      <210> 118
      <211> 71
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(71)
      <223> n = A, T, C \text{ or } G
      <400> 118
                                                                           60
accaaggtgt ntgaatetet gacgtgggga tetetgatte cegeacaate tgagtggaaa
                                                                           71
aantcctqqg t
      <210> 119
      <211> 212
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (212)
      <223> n = A, T, C \text{ or } G
      <400> 119
actocggttg gtgtcagcag cacgtggcat tgaacatngc aatgtggagc ccaaaccaca
                                                                           60
gaaaatgggg tgaaattggc caactttcta tnaacttatg ttggcaantt tgccaccaac
                                                                          120
agtaagctgg cccttctaat aaaagaaaat tgaaaggttt ctcactaanc ggaattaant
                                                                          180
                                                                          212
aatggantca aganacteee aggeeteage gt
      <210> 120
      <211> 90
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(90)
      <223> n = A, T, C or G
      <400> 120
actcgttgca natcaggggc cccccagagt caccgttgca ggagtccttc tggtcttgcc
                                                                           60
                                                                           90
ctccgccggc gcagaacatg ctggggtggt
      <210> 121
       <211> 218
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1) ... (218)
       <223> n = A, T, C \text{ or } G
       <400> 121
                                                                           60
tqtancqtga anacqacaga nagggttqtc aaaaatggag aanccttgaa gtcattttga
                                                                           120
gaataagatt tgctaaaaga tttggggcta aaacatggtt attgggagac atttctgaag
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atatncangt aaattangga atgaattcat gg agcatanact tcatgtgggg atancagcta co	ttcttttg ggaattcctt cttgta	tacgatngcc	180 218
<210> 122		• •	
<211> 171		,	
<212> DNA <213> Homo sapien			
<400> 122			
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catttgttag ctcatggaac aggaagtcgg at	ggtggggc atcttcagtg	ctgcatgagt	120
caccaccccg gcggggtcat ctgtgccaca gg	tccctgtt gacagtgcgg	t	171
<210> 123			
<211> 76			
<212> DNA <213> Homo sapien			
· <220>			
<221> misc_feature <222> (1)(76)	•		
$\langle 223 \rangle$ n = A,T,C or G			
1400 100			
<pre>&lt;400&gt; 123 tgtagcgtga agacnacaga atggtgtgtg ct</pre>	ntoctato caggaacaca	tttattatca	60
ttatcaanta ttgtgt	, ry ruce cay y a caca	cccaccacca	76
<210> 124		#	
<211> 131		•	
<212> DNA <213> Homo sapien			
12132 Homo Sapien	•		
<400> 124			
acctttcccc aaggccaatg tcctgtgtgc taaccaatgtgctg ggtcatatgg aggggaggag ac	ctggccg gctgcaggac	agctgcaatt	130
ttaagatttg t	ccaaaac ayccaaccc	accecetigg	120 131
<210> 125			
<211> 432			-
<212> DNA	•	1	
<213> Homo sapien			•
<400> 125			
actttatcta ctggctatga aatagatggt gga	aaattgc gttaccaact	ataccactgg	60
cttgaaaaag aggtgatagc tetteagagg act etacagtetg catttggeag aaatgaagat gaa	tgtgact tttgctcaga	tgctgaagaa	120
ttgcctcacc aaacaaaagt gaaacaactg aga	gaaaatt ttcaggaaaa	aagacagtgg	180 240
ctcttgaagt atcagtcact tttgagaatg ttt	cttagtt actgcatact	tcatqqatcc	300
catggtgggg gtcttgcatc tgtaagaatg gaa	ttgattt tgcttttgca	agaatctcag	360
caggaaacat cagaaccact attttctage ect ctctttgctt qt	cigicag agcaaacete a	agtgcctctc	420 432
<210> 126 <211> 112			
<211> 112 <212> DNA			
<213> Homo sapien			
<400> 126			
acacaacttg aatagtaaaa tagaaactga gct	gaaattt ctaattcact t	tctaaccat	60
agtaagaatg atatttcccc ccagggatca cca	aatattt ataaaaattt 🤉	gt	112
<210> 127			

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<211> 54
      <212> DNA
      <213> Homo sapien
      <400> 127
                                                                         54
accacqaaac cacaaacaag atggaagcat caatccactt gccaagcaca gcag
      <210> 128
      <211> 323
      <212> DNA
      <213> Homo sapien
      <400> 128
acctcattag taattgtttt gttgtttcat ttttttctaa tgtctcccct ctaccagctc
                                                                         60
acctgagata acagaatgaa aatggaagga cagccagatt teteetttge tetetgetea
                                                                        120
ttctctctga agtctaggtt acccattttg gggacccatt ataggcaata aacacagttc
                                                                        180
ccaaagcatt tggacagttt cttgttgtgt tttagaatgg ttttcctttt tcttagcctt
                                                                        240
ttcctgcaaa aggctcactc agtcccttgc ttgctcagtg gactgggctc cccagggcct
                                                                        300
aggetgeett etttteeatg tee
                                                                        323
      <210> 129
      <211> 192
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(192)
      <223> n = A, T, C or G
      <400> 129
acatacatgt gtgtatattt ttaaatatca cttttgtatc actctgactt tttagcatac
                                                                         60
tgaaaacaca ctaacataat ttntgtgaac catgatcaga tacaacccaa atcattcatc
                                                                        120
                                                                        180
tagcacattc atctgtgata naaagatagg tgagtttcat ttccttcacg ttggccaatg
                                                                        192
gataaacaaa gt
      <210> 130
      <211> 362
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (362)
      <223> n = A, T, C or G
      <400> 130
ccctttttta tggaatgagt agactgtatg tttgaanatt tanccacaac ctctttgaca
                                                                         60
tataatgacg caacaaaaag gtgctgttta gtcctatggt tcagtttatg cccctgacaa
                                                                        120
gtttccattg tgttttgccg atcttctggc taatcgtggt atcctccatg ttattagtaa
                                                                        180
ttctgtattc cattttgtta acgcctggta gatgtaacct gctangaggc taactttata
                                                                        240
cttatttaaa agctcttatt ttgtggtcat taaaatggca atttatgtgc agcactttat
                                                                        300
                                                                        360
tgcagcagga agcacgtgtg ggttggttgt aaagctcttt gctaatctta aaaagtaatg
                                                                        362
αa
      <210> 131
      <211> 332
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
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<222> (1)...(332)
       <223> n = A, T, C or G
       <400> 131
 ctttttgaaa gatcgtgtcc actcctgtgg acatcttgtt ttaatggagt ttcccatgca.
                                                                          60
 gtangactgg tatggttgca gctgtccaga taaaaacatt tgaagagctc caaaatgaga
                                                                         120
 gttctcccag gttcgccctg ctgctccaag tctcagcagc agcctctttt aggaggcatc
                                                                         180
 ttctgaacta gattaaggca gcttgtaaat ctgatgtgat ttggtttatt atccaactaa
                                                                         240
 cttccatctg ttatcactgg agaaagccca gactccccan gacnggtacg gattgtgggc
                                                                         300
 atanaaggat tgggtgaagc tggcgttgtg gt
                                                                         332
       <210> 132
       <211> 322
       <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (322)
      <223> n = A, T, C or G
      <400> 132
acttttgcca ttttgtatat ataaacaatc ttgggacatt ctcctgaaaa ctaggtgtcc
agtggctaag agaactcgat ttcaagcaat tctgaaagga aaaccagcat gacacagaat
                                                                        120
ctcaaattcc caaacagggg ctctgtggga aaaatgaggg aggacctttg tatctcgggt
                                                                        180
tttagcaagt taaaatgaan atgacaggaa aggettattt atcaacaaag agaagagttg
                                                                        240
ggatgcttct aaaaaaaact ttggtagaga aaataggaat gctnaatcct agggaagcct
                                                                        300
gtaacaatct acaattggtc ca
                                                                        322
      <210> 133
      <211> 278
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(278)
      <223> n = A, T, C or G
      <400> 133
acaagccttc acaagtttaa ctaaattggg attaatcttt ctgtanttat ctgcataatt
                                                                         60
cttgtttttc tttccatctg gctcctgggt tgacaatttg tggaaacaac tctattgcta
                                                                        120
ctatttaaaa aaaatcacaa atctttccct ttaagctatg ttnaattcaa actattcctg
                                                                        180
ctattcctgt tttgtcaaag aaattatatt tttcaaaata tgtntatttg tttgatgggt
                                                                        240
cccacgaaac actaataaaa accacagaga ccagcctg
                                                                        278
      <210> 134
      <211> 121
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(121)
      <223> n = A,T,C or G
      <400> 134
gtttanaaaa cttgtttagc tccatagagg aaagaatgtt aaactttgta ttttaaaaca
                                                                        60
tgattctctg aggttaaact tggttttcaa atgttatttt tacttgtatt ttgcttttgg
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                                                                       121
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<210> 135

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<211> 350
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(350)
      <223> n = A, T, C or G
      <400> 135
acttanaacc atgcctagca catcagaatc cctcaaagaa catcagtata atcctatacc
                                                                            60
atancaaqtq qtqactqqtt aaqcqtqcqa caaaqqtcaq ctqqcacatt acttqtqtqc
                                                                           120
aaacttgata cttttgttct aagtaggaac tagtatacag tncctaggan tggtactcca
                                                                           180
gggtgcccc caactcctgc agccgctcct ctgtgccagn ccctgnaagg aactttcgct
                                                                           240
ccacctcaat caagecetgg gecatgetae etgeaattgg etgaacaaac gtttgetgag
                                                                           300
                                                                           350
ttcccaaqqa tqcaaaqcct qqtqctcaac tcctggggcg tcaactcagt
      <210> 136
      <211> 399
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(399)
      <223> n = A, T, C or G
      <400> 136
                                                                            60
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                                                                           120
gctqtqattq tatccqaata ntcctcqtqa qaaaagataa tgagatgacq tgagcagcct
gcagacttgt gtctgccttc aanaagccag acaggaaggc cctgcctgcc ttggctctga
                                                                           180
cctggcggcc agccagccag ccacaggtgg gcttcttcct tttgtggtga caacnccaag aaaactgcag aggcccaggg tcaggtgtna gtgggtangt gaccataaaa caccaggtgc
                                                                           240
                                                                           300
                                                                           360
teccaggaac eegggcaaag gecatececa eetacageca geatgeecae tggegtgatg
                                                                           399
ggtgcagang gatgaagcag ccagntgttc tgctgtggt
      <210> 137
      <211> 165
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (165)
      <223> n = A, T, C or G
      <400> 137
                                                                             60
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ggaggaagtg tgtgaacgta gggatgtaga ngttttggcc gtgctaaatg agcttcggga
                                                                           120
                                                                           165
ttggctggtc ccactggtgg tcactgtcat tggtggggtt cctgt
      <210> 138
      <211> 338
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(338)
      <223> n = A, T, C or G
      <400> 138
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actcactgga atgccacatt cacaacagaa tcagaggtct gtgaaaacat taatggctcc

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ttaacttctc cagtaagaat cagggacttg aaatggaaac gttaacagcc acatgcccaa
                                                                        120
tgctgggcag tctcccatgc cttccacagt gaaagggctt gagaaaaatc acatccaatg
                                                                        180
tcatgtgttt ccagccacac caaaaggtgc ttggggtgga gggctggggg catananggt
                                                                        240
cangceteag gaageeteaa gtteeattea getttgeeae tgtacattee ceatntttaa
                                                                        300
aaaaactgat gccttttttt tttttttttg taaaattc
                                                                        338
      <210> 139
      <211> 382
      <212> DNA
      <213> Homo sapien
      <400> 139
gggaatcttg gtttttggca tctggtttgc ctatagccga ggccactttg acagaacaaa
                                                                         60
gaaagggact tcgagtaaga aggtgattta cagccagcct agtgcccgaa gtgaaggaga
                                                                        120
attcaaacag acctcgtcat tcctggtgtg agcctggtcg gctcaccgcc tatcatctgc
                                                                        180
atttgcctta ctcaggtgct accggactct ggcccctgat gtctgtagtt tcacaggatg
                                                                        240
cettatttgt cttctacacc ccacagggcc ccctacttct tcggatgtgt ttttaataat
                                                                        300
gtcagctatg tgccccatcc tccttcatgc cctccctccc tttcctacca ctgctgagtg
                                                                        360
gcctggaact tgtttaaagt gt
                                                                        382
      <210> 140
      <211> 200
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(200)
      <223> n = A, T, C or G
accaaanctt ctttctgttg tgttngattt tactataggg gtttngcttn ttctaaanat
                                                                         60
acttttcatt taacancttt tgttaagtgt caggctgcac tttgctccat anaattattg
                                                                        120
ttttcacatt tcaacttgta tgtgtttgtc tcttanagca ttggtgaaat cacatatttt
                                                                        180
atattcagca taaaggagaa
                                                                        200
      <210> 141
      <211> 335
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(335)
      <223> n = A, T, C or G
      <400> 141
actitattit caaaacactc atatgitgca aaaaacacat agaaaaataa agiittggtgg
                                                                         60
gggtgctgac taaacttcaa gtcacagact tttatgtgac agattggagc agggtttgtt
                                                                        120
atgcatgtag agaacccaaa ctaatttatt aaacaggata gaaacaggct gtctgggtga
                                                                       180
aatggttetg agaaceatee aatteaeetg teagatgetg atanaetage tetteagatg
                                                                        240
tttttctacc agttcagaga tnggttaatg actanttcca atggggaaaa agcaagatgg
                                                                        300
attcacaaac caagtaattt taaacaaaga cactt
                                                                        335
      <210> 142
      <211> 459
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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<220>

<222> (1)...(459) <223> n = A, T, C or G<400> 142 accaggttaa tattgccaca tatatccttt ccaattgcgg gctaaacaga cgtgtattta gggttgttta aagacaaccc agcttaatat caagagaaat tgtgaccttt catggagtat 60 120 ctgatggaga aaacactgag ttttgacaaa tcttatttta ttcagatagc agtctgatca 180 cacatogtec aacaacacte aaataataaa teaaatatna teagatgtta aagattggte 240 ttcaaacatc atagccaatg atgccccgct tgcctataat ctctccgaca taaaaccaca 300 tcaacacctc aqtqqccacc aaaccattca qcacagcttc cttaactgtg agctgtttga 360 agctaccagt ctgagcacta ttgactatnt ttttcangct ctgaatagct ctagggatct 420 459 cagcangggt gggaggaacc agctcaacct tggcgtant <210> 143 <211> 140 <212> DNA <213> Homo sapien <400> 143 acattteett ceaceaagte aggacteetg gettetgtgg gagttettat cacetgaggg 60 aaatccaaac agtototoot agaaaggaat agtgtcacca accccaccca totocotgag 120 140 accatccgac ttccctqtgt <210> 144 <211> 164 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1) ... (164) <223> n = A, T, C or G<400> 144 acttcagtaa caacatacaa taacaacatt aagtgtatat tgccatcttt gtcattttct 60 atctatacca ctctcccttc tgaaaacaan aatcactanc caatcactta tacaaatttg 120 aggcaattaa tocatatttg tittcaataa ggaaaaaaag atgt 164 <210> 145 <211> 303 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1)...(303) <223> n = A, T, C or G<400> 145 acgtagacca tocaactttg tatttgtaat ggcaaacatc cagnagcaat toctaaacaa 60 actggagggt atttataccc aattatccca ttcattaaca tgccctcctc ctcaggctat 120 gcaggacagc tatcataagt cggcccaggc atccagatac taccatttgt ataaacttca 180 gtaggggagt ccatccaagt gacaggtcta atcaaaggag gaaatggaac ataagcccag 240 300 tagtaaaatn ttgcttagct gaaacagcca caaaagactt accgccgtgg tgattaccat 303 caa <210> 146 <211> 327 <212> DNA <213> Homo sapien

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<221> misc_feature
       <222> (1) ... (327)
       <223> n = A, T, C or G
       <400> 146
actgcagctc aattagaagt ggtctctgac tttcatcanc ttctccctgg gctccatgac
actggcctgg agtgactcat tgctctggtt ggttgagaga gctcctttgc caacaggcct
                                                                        120
ccaagtcagg gctgggattt gtttcctttc cacattctag caacaatatg ctggccactt
                                                                        180
cctgaacagg gagggtggga ggagccagca tggaacaagc tgccactttc taaagtagcc
                                                                        240
agacttgccc ctgggcctgt cacacctact gatgaccttc tqtqcctqca qqatqqaatq
                                                                        300
taggggtgag ctgtgtgact ctatggt
                                                                        327
       <210> 147
      <211> 173
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (173)
      <223> n = A, T, C or G
      <400> 147
acattgtttt tttgagataa agcattgana gagctctcct taacqtgaca caatggaagg
                                                                         60
actggaacac atacccacat ctttgttctg agggataatt ttctgataaa qtcttqctgt
                                                                        120
atattcaagc acatatgtta tatattattc agttccatgt ttatagccta gtt
                                                                        173
      <210> 148
      <211> 477
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (477)
      <223> n = A, T, C or G
      <400> 148
acaaccactt tatctcatcg aatttttaac ccaaactcac tcactgtgcc tttctatcct
                                                                         60
atgggatata ttatttgatg ctccatttca tcacacatat atgaataata cactcatact
                                                                        120
geoctactae etgetgeaat aateacatte cetteetgte etgaceetga agecattggg
                                                                        180
gtggtcctag tggccatcag tccangcctg caccttgagc ccttgagctc cattgctcac
                                                                        240
nccancecae etcacegace ceatectett acacagetae etcettgete tetaacecea
                                                                        300
tagattatnt ccaaattcag tcaattaagt tactattaac actctacccg acatgtccag
                                                                        360
caccactggt aagcettete cagecaacae acacacaca acacneacae acacacatat
                                                                        420
ccaggcacag gctacctcat cttcacaatc acccctttaa ttaccatgct atggtgg
                                                                        477
      <210> 149
      <211> 207
      <212> DNA
      <213> Homo sapien
      <400> 149
acagttgtat tataatatca agaaataaac ttgcaatgag agcatttaag agggaagaac
                                                                         60
taacgtattt tagagagcca aggaaggttt ctgtggggag tgggatgtaa ggtggggcct
                                                                        120
gatgataaat aagagtcagc caggtaagtg ggtggtgtgg tatgggcaca gtgaagaaca
                                                                        180
tttcaggcag agggaacagc agtgaaa
                                                                        207
      <210> 150
      <211> 111
      <212> DNA -
      <213> Homo sapien
```

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<220>
      <221> misc_feature
      <222> (1)...(111)
      <223> n = A, T, C or G
      <400> 150
accttgattt cattgctgct ctgatggaaa cccaactatc taatttagct aaaacatggg
                                                                         60
cacttaaatg tggtcagtgt ttggacttgt taactantgg catctttggg t
      <210> 151
      <211> 196
      <212> DNA
      <213> Homo sapien
      <400> 151
agegeggeag gteatattga acatteeaga tacetateat tactegatge tgttgataac
                                                                         60
agcaagatgg ctttgaactc agggtcacca ccagctattg gaccttacta tgaaaaccat
                                                                        120
                                                                        180
ggataccaac cggaaaaccc ctatcccgca cagcccactg tggtccccac tgtctacgag
                                                                        196
gtgcatccgg ctcagt
      <210> 152
      <211> 132
      <212> DNA
      <213> Homo sapien
      <400> 152
                                                                        60
acagcacttt cacatgtaag aagggagaaa ttcctaaatg taggagaaag ataacagaac
cttccccttt tcatctagtg gtggaaacct gatgctttat gttgacagga atagaaccag
                                                                       120
                                                                        132
gagggagttt gt
      <210> 153
      <211> 285
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(285)
      <223> n = A, T, C or G
      <400> 153
acaanaccca nganaggcca etggccgtgg tgtcatggcc tccaaacatg aaagtgtcag
cttctqctct tatqtcctca tctqacaact ctttaccatt tttatcctcg ctcagcagga
                                                                        120
qcacatcaat aaaqtccaaa qtcttggact tggccttggc ttggaggaag tcatcaacac
                                                                        180
                                                                        240
cctggctagt gagggtgcgg cgccgctcct ggatgacggc atctgtgaag tcgtgcacca
                                                                        285
gtctgcaggc cctgtggaag cgccgtccac acggagtnag gaatt
      <210> 154
      <211> 333
      <212> DNA
      <213> Homo sapien
      <400> 154
accacagtcc tgttgggcca gggcttcatg accctttctg tgaaaagcca tattatcacc
                                                                         60
                                                                        120
accccaaatt tttccttaaa tatctttaac tgaaggggtc agcctcttga ctgcaaagac
cctaagccgg ttacacagct aactcccact ggccctgatt tgtgaaattg ctgctgcctg
                                                                        180
attggcacag gagtcgaagg tgttcagctc ccctcctccg tggaacgaga ctctgatttg
                                                                        240
                                                                        300
aqtttcacaa attctcgggc cacctcgtca ttgctcctct gaaataaaat ccggagaatg
gtcaggcctg tctcatccat atggatcttc cgg
                                                                        333
```

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<211> 308
       <212> DNA
       <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (308)
      <223> n = A, T, C or G
      <400> 155
actggaaata ataaaaccca catcacagtg ttgtgtcaaa gatcatcagg gcatggatgg
                                                                         60
gaaagtgctt tgggaactgt aaagtgccta acacatgatc gatgattttt gttataatat
                                                                        120
ttgaatcacg gtgcatacaa actotoctgc ctgctcctcc tgggccccag ccccagcccc
                                                                        180
atcacagete actgetetgt teatecagge ecageatgta gtggetgatt ettettgget
                                                                        240
gettttagee tecanaagtt tetetgaage caaccaaace tetangtgta aggeatgetg
                                                                        300
gccctggt
                                                                        308
      <210> 156
      <211> 295
      <212> DNA
      <213> Homo sapien
      <400> 156
accttgctcg gtgcttggaa catattagga actcaaaata tgagatgata acagtgccta
                                                                         60
ttattgatta ctgagagaac tgttagacat ttagttgaag attttctaca caggaactga
                                                                        120
gaataggaga ttatgtttgg coctcatatt ctctcctatc ctccttgcct cattctatgt
                                                                        180
ctaatatatt ctcaatcaaa taaggttagc ataatcagga aatcgaccaa ataccaatat
                                                                        240
aaaaccagat gtctatcctt aagattttca aatagaaaac aaattaacag actat
                                                                        295
      <210> 157
      <211> 126
      <212> DNA
      <213> Homo sapien
      <400> 157
acaagtttaa atagtgctgt cactgtgcat gtgctgaaat gtgaaatcca ccacatttct
                                                                         60
gaagagcaaa acaaattctg tcatgtaatc tctatcttgg gtcgtgggta tatctgtccc
                                                                        120
cttagt
                                                                        126
      <210> 158
      <211> 442
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(442)
      <223> n = A, T, C or G
      <400> 158
acceactggt cttggaaaca cccatcctta atacgatgat ttttctgtcg tgtgaaaatg
                                                                         60
aanccagcag getgeeecta gteagteett eetteeagag aaaaagagat ttgagaaagt
                                                                        120
                                                                        180
gcctgggtaa ttcaccatta atttcctccc ccaaactctc tgagtcttcc cttaatattt
ctggtggttc tgaccaaagc aggtcatggt ttgttgagca tttgggatcc cagtgaagta
                                                                        240
natgitigta gccttgcata citagccctt cccacgcaca aacggagtgg cagagtggtg
                                                                        300
ccaaccctgt tttcccagtc cacgtagaca gattcacagt gcggaattct ggaagctgga
                                                                        360
nacagacggg ctctttgcag agccgggact ctgagangga catgagggcc tctgcctctg
                                                                        420
tgttcattct ctgatgtcct gt
                                                                        442
      <210> 159
      <211> 498
```

<212> DNA

```
<213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(498)
      <223> n = A, T, C or G
      <400> 159
acttecaggt aacgttgttg tttccgttga geetgaactg atgggtgaeg ttgtaggtte
                                                                         60
                                                                        120
tocaacaaga actgaggttg cagagogggt agggaagagt gotgttocag ttgcacotgg
gctgctgtgg actgttgttg attcctcact acggcccaag gttgtggaac tggcanaaag
                                                                        180
gtgtgttgtt gganttgage tegggegget gtggtaggtt gtgggetett caacagggge
                                                                        240
tgctgtggtg ccgggangtg aangtgttgt gtcacttgag cttggccagc tctggaaagt
                                                                        300
antanattct tcctgaaggc cagcgcttgt ggagctggca ngggtcantg ttgtgtgtaa
                                                                       360
cgaaccagtg ctgctgtggg tgggtgtana tcctccacaa agcctgaagt tatggtgtcn
                                                                        420
teaggtaana atgtggttte agtgteett ggengetgtg gaaggttgta nattgteace
                                                                        480
                                                                        498
aagggaataa gctgtggt
      <210> 160
      <211> 380
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (380)
      <223> n = A, T, C or G
      <400> 160
acctgcatec agetteeetg ecaaacteae aaggagacat caacetetag acagggaaac
                                                                        60
                                                                        120
agetteagga tacttecagg agacagagee accageagea aaacaaatat teecatgeet
ggagcatggc atagaggaag ctganaaatg tggggtctga ggaagccatt tgagtctggc
                                                                        180
cactagacat ctcatcagcc acttgtgtga agagatgccc catgacccca gatgcctctc
                                                                        240
ccaccettac etecatetea cacaettgag etttecaete tgtataatte taacateetg
                                                                       300
                                                                       360
qaqaaaaatq qcaqtttqac cqaacctqtt cacaacggta gaggctgatt tctaacgaaa
                                                                        380
cttgtagaat gaagcctgga
      <210> 161
      <211> 114
      <212> DNA
      <213> Homo sapien
      <400> 161
actocacate coetetgage aggeggttgt cgttcaaggt gtatttggcc ttqcctgtca
                                                                        60
cactgtccac tggcccctta tccacttggt gcttaatccc tcgaaagagc atgt
                                                                        114
      <210> 162
      <211> 177
      <212> DNA
      <213> Homo sapien
      <400> 162
actttctqaa tcqaatcaaa tgatacttag tgtagtttta atatcctcat atatatcaaa
                                                                        60
                                                                       120
qttttactac tctgataatt ttgtaaacca ggtaaccaga acatccagtc atacagcttt
tggtgatata taacttggca ataacccagt ctggtgatac ataaaactac tcactgt
                                                                        177
      <210> 163
      <211> 137
      <212> DNA
      <213> Homo sapien
      <220>
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```
<221> misc_feature
       <222> (1) ... (137)
       <223> n = A, T, C or G
       <400> 163
 catttataca gacaggcgtg aagacattca cgacaaaaac gcgaaattct atcccgtqac
 canagaagge agetacgget actectacat cetggegtgg gtggeetteg cetgeacett
                                                                         120
 catcagcggc atgatgt
                                                                         137
       <210> 164
       <211> 469
       <212> DNA
       <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (469)
      <223> n = A, T, C or G
      <400> 164
cttatcacaa tgaatgttct cctgggcagc gttgtgatct ttgccacctt cgtgacttta
                                                                         60
tgcaatgcat catgctattt catacctaat gagggagttc caggagattc aaccaggaaa
                                                                        120
tgcatggatc tcaaaggaaa caaacaccca ataaactcqq aqtqqcaqac tqacaactqt
                                                                        180
gagacatgca cttgctacga aacagaaatt tcatgttgca cccttgttc tacacctgtg
                                                                        240
ggttatgaca aagacaactg ccaaagaatc ttcaagaagg aggactgcaa gtatatcgtg
                                                                        300
gtggagaaga aggacccaaa aaagacctgt tctgtcagtg aatggataat ctaatgtgct
                                                                        360
totagtaggc acagggetee caggecagge etcattetee tetggeetet aatagteaat
                                                                        420
gattgtgtag ccatgcctat cagtaaaaag atntttgagc aaacacttt
                                                                        469
      <210> 165
     · <211> 195
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(195)
      <223> n = A, T, C or G
      <400> 165
acagtttttt atanatatcg acattgccgg cacttgtgtt cagtttcata aagctggtgg
                                                                         60
atcogctgtc atcoactatt cottggctag agtaaaaatt attottatag cocatgtccc
                                                                        120
tgcaggccgc ccgcccgtag ttctcgttcc agtcgtcttg gcacacaggg tgccaggact
                                                                        180
tcctctgaga tgagt
                                                                        195
      <210> 166
      <211> 383
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(383)
      <223> n = A, T, C or G
      <400> 166
acatettagt agtgtggeae ateaggggge cateagggte acagteacte atageetege
                                                                         60
cgaggtcgga gtccacacca ccggtgtagg tgtgctcaat cttgggcttg gcgcccacct
                                                                        120
ttggagaagg gatatgctgc acacacatgt ccacaaagcc tgtgaactcg ccaaagaatt
                                                                        180
tttgcagacc agcctgagca aggggcggat gttcagcttc agctcctcct tcgtcaggtg
                                                                        240
gatgecaace tegtetangg teegtgggaa getggtgtee aenteaceta caacetggge
                                                                        300
gangatetta taaagagget eenagataaa eteeacgaaa ettetetggg agetgetagt
                                                                        360
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nggggccttt ttggtgaact ttc
                                                                        383
      <210> 167
      <211> 247
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (247)
      <223> n = A, T, C or G
      <400> 167
acagagecag acettggeca taaatgaanc agagattaag actaaacece aagteganat
                                                                         60
tggagcagaa actggagcaa gaagtgggcc tggggctgaa gtagagacca aggccactgc
                                                                        120
tatanccata cacagageca acteteagge caaggenatg gttggggeag anceagagae
                                                                        180
tcaatctgan tccaaagtgg tggctggaac actggtcatg acanaggcag tgactctgac
                                                                        240
tgangtc
                                                                        247
      <210> 168 <211> 273
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (273)
      <223> n = A, T, C or G
      <400> 168
acttetaagt tttetagaag tggaaggatt gtanteatee tgaaaatggg tttactteaa
                                                                         60
aatccctcan cettgttett cacnactgte tatactgana gtgtcatgtt tecacaaagg
                                                                        120
gctgacacct gagcctgnat tttcactcat ccctgagaag ccctttccag tagggtgggc
                                                                        180
aatteecaae tteettgeea caagetteee aggetttete eeetggaaaa eteeagettg
                                                                        240
agtoccagat acactcatgg gctgccctgg gca
                                                                        273
      <210> 169
      <211> 431
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (431)
      <223> n = A, T, C or G
      <400> 169
acageettgg etteeceaaa eteeacagte teagtgeaga aagateatet teeageagte
                                                                         60
ageteagace agggteaaag gatgtgacat caacagttte tggtttcaga acaggtteta
                                                                        120
ctactgtcaa atgaccccc atacttcctc aaaggctgtg gtaagttttg cacaggtgag
                                                                        180
ggcagcagaa agggggtant tactgatgga caccatcttc tctgtatact ccacactgac
                                                                        240
cttgccatgg gcaaaggccc ctaccacaaa aacaatagga tcactgctgg gcaccagctc
                                                                        300
acquacatca ctgacaaccq qqatqgaaaa aqaantqcca actttcatac atccaactqq
                                                                        360
                                                                        420
aaagtgatct gatactggat tettaattae etteaaaage ttetggggge cateagetge
                                                                        431
tcgaacactg a
      <210> 170
      <211> 266
      <212> DNA
      <213> Homo sapien
      <220>
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<221> misc_feature
       <222> (1)...(266)
       <223> n = A,T,C or G
       <400> 170
acctgtgggc tgggctgtta tgcctgtgcc ggctgctgaa agggagttca gaggtggagc
                                                                            60
tcaaggaget etgeaggeat tttgecaane etetecanag canagggage aacetacaet
                                                                           120
ccccgctaga aagacaccag attggagtcc tgggaggggg agttggggtg ggcatttgat
                                                                           180
gtatacttgt cacctgaatg aangagccag agaggaanga gacgaanatg anattggcct
                                                                           240
                                                                           266
tcaaagctag gggtctggca ggtgga
       <210> 171
       <211> 1248
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(1248)
       <223> n = A, T, C \text{ or } G
       <400> 171
qqcaqccaaa tcataaacqq cqaqqactqc aqcccqcact cqcaqccctq qcaqqcqca
                                                                            60
ctggtcatgg aaaacgaatt gttctgctcg ggcgtcctgg tgcatccgca gtgggtgctg
                                                                          120
tcagccgcac actgtttcca gaagtgagtg cagagctcct acaccatcgg gctgggcctg
                                                                          180
cacagtettg aggeegaeca agageeaggg ageeagatgg tggaggeeag ceteteegta
                                                                          240
eggeacecag agtacaacag accettgete getaacgace teatgeteat caagttggac
                                                                          300
gaatcogtgt cogagtotga caccatoogg agcatoagca ttgottogca gtgocotaco
                                                                          360
gcggggaact cttgcctcgt ttctggctgg ggtctgctgg cgaacggcag aatgcctacc gtgctgcagt gcgtgaacgt gtcggtggtg tctgaggagg tctgcagtaa gctctatgac ccgctgtacc accccagcat gttctgcgcc ggcggagggc aagaccagaa ggactcctgc
                                                                          420
                                                                          480
                                                                          540
aacggtgact ctggggggcc cctgatctgc aacgggtact tgcagggcct tgtgtctttc
                                                                          600
qqaaaagccc cqtqtqqcca agttqqcqtq ccagqtqtct acaccaacct ctqcaaattc
                                                                          660
actgagtgga tagagaaaac cgtccaggcc agttaactct ggggactggg aacccatgaa
                                                                          720
attgacccc aaatacatcc tgcggaagga attcaggaat atctgttccc agcccctcct
                                                                          780
                                                                          840
coctcaggoe caggagtoca ggoecocago coctcotoco toaaaccaag ggtacagato
cccaqccct cctccctcaq acccaqqagt ccagacccc cagccctcc tccctcagac
                                                                          900
                                                                          960
ccaggagtec agecectect cecteagace caggagteca gaccececag ecectectec
ctcagaccca ggggtccagg cccccaaccc ctcctccctc agactcagag gtccaagccc
                                                                         1020
ccaaccente attecccaga cccagaggte caggteccag ecetentee etcagaccea
                                                                         1080
geggteeaat gecaectaga ethteeetgt acacagtgee eeettgtgge aegttgaeee
                                                                         1140
                                                                         1200
aaccttacca gttggttttt catttttngt ccctttcccc tagatccaga aataaagttt
1248
      <210> 172°
      <211> 159
      <212> PRT
      <213> Homo sapien
      <220>
      <221> VARIANT
      <222> (1)...(159)
      <223> Xaa = Any Amino Acid
      <400> 172
Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro
                                      10
Leu Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser
                                  25
Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr
                              40
Ala Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly
```

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```
50
                         55
Arg Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu
65
Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe
                                      90
                 85
Cys Ala Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser
             100
                                  105
                                                       110
Gly Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe
        115
                             120
                                                   125
Gly Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn
                         135
Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
                     150
                                          155
       <210> 173
      <211> 1265
       <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(1265)
      <223> n = A, T, C or G
      <400> 173
ggcagcccgc actcgcagcc ctggcaggcg gcactggtca tggaaaacga attgttctgc
togggcgtcc tggtgcatcc gcagtgggtg ctgtcagccg cacactgttt ccagaactcc
                                                                          120
tacaccatcg ggctgggcct gcacagtctt gaggccgacc aagagccagg gagccagatg
                                                                          180
gtggaggcca gcctctccgt acggcaccca gagtacaaca gacccttgct cqctaacqac
                                                                          240
ctcatgctca tcaagttgga cgaatccgtg tccgagtctg acaccatccg gagcatcagc
                                                                          300
attgcttcgc agtgccctac cgcggggaac tcttgcctcg tttctggctg gggtctgctg
                                                                          360
gegaacggtg ageteacggg tgtgtgtetg ceetetteaa ggaggteete tgeecagteg egggggetga ceeagagete tgegteecag geagaatgee tacegtgetg eagtgegtga
                                                                          420
                                                                          480
acgtgtcggt ggtgtctgag gaggtctgca gtaagctcta tgacccgctg taccacccca
                                                                          540
gcatgttctg cgccggcgga gggcaagacc agaaggactc ctgcaacggt gactctgggg
                                                                          600
ggcccctgat ctgcaacggg tacttgcagg gccttgtgtc tttcggaaaa gccccgtgtg
                                                                          660
gccaagttgg cgtgccaggt gtctacacca acctctgcaa attcactgag tggatagaga
                                                                          720
aaaccgtcca ggccagttaa ctctggggac tgggaaccca tgaaattgac ccccaaatac
                                                                          780
atcetgegga aggaatteag gaatatetgt teecageeee teeteeetea ggeeeaggag
                                                                          840
tocaggecce cagecectee teecteaaac caagggtaca gatececage ecetectee
                                                                          900
tcagacccag gagtccagac cccccagccc ctcctccctc agacccagga gtccagccc
                                                                          960
tecteentea gacceaggag tecagaceee ceageceete eteceteaga eecaggggtt
                                                                         1020
gaggeeecca accectecte etteagagte agaggteeaa geeeccaace cetegtteee
                                                                         1080
cagacccaga ggtnnaggtc ccagcccctc ttccntcaga cccagnggtc caatgccacc
                                                                         1140
tagattttcc ctgnacacag tgcccccttg tggnangttg acccaacctt accagttggt
                                                                        1200
ttttcatttt tngtcccttt cccctagatc cagaaataaa gtttaagaga ngngcaaaaa
                                                                        1260
aaaaa
                                                                         1265
      <210> 174
      <211> 1459
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(1459)
      <223> n = A, T, C \circ G
      <400> 174
ggtcagccgc acactgtttc cagaagtgag tgcagagctc ctacaccatc gggctgggcc
                                                                           60
tgcacagtct tgaggccgac caagagccag ggagccagat ggtggaggcc agcctctccg
                                                                         120
tacggcaccc agagtacaac agaccettgc tegetaacga ceteatgete atcaagttgg
```

```
acgaatccgt gtccgagtct gacaccatcc ggagcatcag cattgcttcg cagtgcccta
                                                                        240
                                                                        300
ccgcggggaa ctcttgcctc gtttctggct ggggtctgct ggcgaacggt gagctcacgg
gtgtgtgtct gccctcttca aggaggtcct ctgcccaqtc gcgggggctq acccaqagct
                                                                        360
                                                                        420
ctgcgtccca ggcagaatgc ctaccgtgct gcagtgcgtg aacgtgtcgg tggtgtctga
                                                                        480
ngaggtetge antaagetet atgaceeget gtaceaeee ancatgttet gegeeggegg
agggcaagac cagaaggact cctgcaacgt gagagagggg aaaggggagg gcaggcgact
                                                                        540
cagggaaggg tggagaaggg ggagacagag acacacaggg ccgcatggcg agatgcagag
                                                                        600
atggagagac acacagggag acagtgacaa ctagagagag aaactgagag aaacagagaa
                                                                        660
                                                                        720
ataaacacag gaataaagag aagcaaagga agagagaaac agaaacagac atggggaggc
                                                                        780
agaaacacac acacatagaa atgcagttga ccttccaaca gcatggggcc tgagggcggt
gacctccacc caatagaaaa teetettata aettttgaet eeccaaaaac etgactagaa
                                                                        840
atagectact gttgaegggg ageettacea ataacataaa tagtegattt atgeatacgt
                                                                        900
tttatgcatt catgatatac ctttgttgga attttttgat atttctaagc tacacagttc
                                                                        960
gtotgtgaat ttttttaaat tgttgcaact ctoctaaaat ttttctgatg tgtttattga
                                                                       1020
aaaaatccaa gtataagtgg acttgtgcat tcaaaccagg gttgttcaag ggtcaactgt
                                                                       1080
gtacccagag ggaaacagtg acacagattc atagaggtga aacacgaaga gaaacaggaa
                                                                      1140
aaatcaagac totacaaaga ggotgggcag ggtggctcat gcotgtaatc ccagcacttt
                                                                       1200
qqqaqqcqaq qcaqqcaqat cacttqaqqt aaggagttca agaccagcct qqccaaaatq
                                                                       1260
gtgaaatcct gtctgtacta aaaatacaaa agttagctgg atatggtggc aggcgcctgt
                                                                      1320
aatcccagct acttgggagg ctgaggcagg agaattgctt gaatatggga ggcagaggtt
                                                                      1380
                                                                       1440
gaagtgagtt gagatcacac cactatactc cagetggggc aacagagtaa gactetgtet
caaaaaaaaa aaaaaaaaa
                                                                       1459
      <210> 175
      <211> 1167
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(1167)
      <223> n = A, T, C or G
      <400> 175
gegeageest ggeaggegge actggteatg gaaaacgaat tgttetgete gggegteetg
                                                                        60
gtgcatccgc agtgggtgct gtcagccgca cactgtttcc agaactccta caccatcggg
                                                                       120
                                                                       180
ctgggcctgc acagtettga ggccgaccaa gagccaggga gccagatggt ggaggccagc
ctctccgtac ggcacccaga gtacaacaga ctcttgctcg ctaacgacct catgctcatc
                                                                       240
aagttggacg aatccgtgtc cgagtctgac accatccgga gcatcagcat tgcttcgcag
                                                                       300
tgccctaccg cggggaactc ttgcctcgtn tctggctggg gtctgctggc gaacggcaga
                                                                       360
atgcctaccg tgctgcactg cgtgaacgtg tcggtggtgt ctgaggangt ctgcagtaag
                                                                       420
ctctatgacc cgctgtacca ccccagcatg ttctgcgccg gcggagggca agaccagaag
                                                                       480
gactectgca aeggtgacte tggggggeee etgatetgca aegggtactt geagggeett
                                                                       540
                                                                       600
gtgtctttcg gaaaagecce gtgtggccaa ettggcgtgc caggtgtcta caccaacete
tqcaaattca ctgagtqgat agagaaaacc qtccagncca gttaactctg qqqactqqqa
                                                                       660
acceatgaaa ttgaceeeca aatacateet geggaangaa tteaggaata tetgtteeca
                                                                       720
                                                                       780
gecetecte ecteaggeee aggagteeag geceeeagee ectecteet caaaceaagg
gtacagated coagedecte eteceteaga cocaggagte cagacedece agedectent
                                                                       840
contragace caggagica geocetecte entragarge aggagicas acceccage
                                                                       900
cententeeg teagacecag gggtgeagge ecceaacece tenteentea gagteagagg
                                                                       960
tecaageece caaceeteg ttececagae ceagaggtne aggteecage eceteeteec
                                                                      1020
tcagacccag cggtccaatg ccacctagan tntccctgta cacagtgccc ccttgtggca
                                                                      1080
ngttgaccca accttaccag ttggtttttc atttttgtc cctttcccct agatccagaa
                                                                      1140
ataaagtnta agagaagcgc aaaaaaa
                                                                      1167
      <210> 176
      <211> 205
      <212> PRT
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<221> VARIANT

<220>

<213> Homo sapien

<222> (1)...(205) <223> Xaa = Any Amino Acid

<400> 176 Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val-35 40 Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Leu Leu Leu 55 Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser 70 Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met 100 105 110 Pro Thr Val Leu His Cys Val Asn Val Ser Val Val Ser Glu Xaa Val 120 125 Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala 130 135 140 Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly 150 155 Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys 170 175 165 Ala Pro Cys Gly Gln Leu Gly Val Pro Gly Val Tyr Thr Asn Leu Cys 180 185 Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Xaa Ser 200 205

<210> 177 <211> 1119 <212> DNA <213> Homo sapien

<400> 177

gcgcactcgc agccctggca ggcggcactg gtcatggaaa acgaattgtt ctgctcgggc 60 gtcctggtgc atccgcagtg ggtgctgtca gccgcacact gtttccagaa ctcctacacc 120 ategggetgg geetgeacag tettgaggee gaccaagage cagggageea gatggtggag 180 gccagcctct ccgtacggca cccagagtac aacagaccct tgctcgctaa cgacctcatg 240 ctcatcaagt tggacgaatc cgtgtccgag tctgacacca tccggagcat cagcattgct 300 tegeagtgcc ctacegeggg gaactettgc etegtttetg getggggtet getggegaac 360 gatgetgtga ttgccatcca gtcccagact gtgggagget gggagtgtga gaagetttcc 420 caaccetgge agggttgtac cattteggea acttecagtg caaggaegte etgetgeate 480 ctcactgggt gctcactact gctcactgca tcacccggaa cactgtgatc aactagccag 540 caccatagtt ctccgaagtc agactatcat gattactgtg ttgactgtgc tgtctattgt 600 actaaccatg ccgatgttta ggtgaaatta gcgtcacttg gcctcaacca tcttggtatc 660 cagttatect cactgaattg agattteetg etteagtgte agecatteee acataattte 720 780 tgacctacag aggtgaggga tcatatagct cttcaaggat gctggtactc ccctcacaa ttcatttctc ctgttgtagt gaaaggtgcg ccctctggag cctcccaggg tgggtgtgca 840 ggtcacaatg atgaatgtat gatcgtgttc ccattaccca aagcctttaa atccctcatg 900 ctcagtacac cagggcaggt ctagcatttc ttcatttagt gtatgctgtc cattcatgca 960 accacctcag gactcctgga ttctctgcct agttgagctc ctgcatgctg cctccttggg 1020 1080 gaggtgaggg agagggccca tggttcaatg ggatctgtgc agttgtaaca cattaggtgc ttaataaaca gaagctgtga tgttaaaaaa aaaaaaaaa 1119

<210> 178 <211> 164 <212> PRT

<213> Homo sapien

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<220>
      <221> VARIANT
      <222> (1)...(164)
      <223> Xaa = Any Amino Acid
      <400> 178
Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp
                                     10
Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu
            20
                                25
Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu
Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
                    70
                                         75
Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
                85
Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Asp Ala Val
                                105
Ile Ala Ile Gln Ser Xaa Thr Val Gly Gly Trp Glu Cys Glu Lys Leu
                                                 125
        115
                            120
Ser Gln Pro Trp Gln Gly Cys Thr Ile Ser Ala Thr Ser Ser Ala Arg
                        135
                                             140
    130
Thr Ser Cys Cys Ile Leu Thr Gly Cys Ser Leu Leu Leu Thr Ala Ser
                                         155
145
Pro Gly Thr Leu
      <210> 179
      <211> 250
      <212> DNA
      <213> Homo sapien
      <400> 179
ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct
                                                                        60
ccagctgccc ccggccgggg gatgcgaggc tcggagcacc cttgcccggc tgtgattgct
                                                                        120
                                                                        180
gccaggcact gttcatctca gcttttctgt ccctttgctc ccggcaagcg cttctgctga
                                                                        240
aagttcatat ctggagcctg atgtcttaac gaataaaggt cccatgctcc acccgaaaaa
aaaaaaaaa
                                                                        250
      <210> 180
      <211> 202
      <212> DNA
      <213> Homo sapien
      <400> 180
                                                                        60
actagtccag tgtggtggaa ttccattgtg ttgggcccaa cacaatggct acctttaaca
teacceagae ecceptecete ecceptece accetete taaccacagt atgatgetta
                                                                       120
ctctgctact cggaaactat ttttatgtaa ttaatgtatg ctttcttgtt tataaatgcc
                                                                        180
                                                                       202
tgatttaaaa aaaaaaaaa aa
      <210> 181
      <211> 558
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(558)
      <223> n = A, T, C or G
```

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<400> 181
tecytttqkt naqqtttkkq aqacameeek aqacetwaan etqtqtcaca qaetteynqq
                                                                             60
aatgtttagg cagtgctagt aatttcytcg taatgattct gttattactt tcctnattct
                                                                            120
ttattcctct ttcttctgaa gattaatgaa gttgaaaatt gaggtggata aatacaaaaa
                                                                            180
ggtagtgtga tagtataagt atctaagtgc agatgaaagt gtgttatata tatccattca
                                                                            240
aaattatgca agttagtaat tactcagggt taactaaatt actttaatat gctgttgaac
                                                                            300
ctactctgtt ccttggctag aaaaaattat aaacaggact ttgttagttt gggaagccaa
                                                                            360
attgataata ttctatgttc taaaagttgg gctatacata aattattaag aaatatggaw
                                                                            420
ttttattccc aggaatatgg kgttcatttt atgaatatta cscrggatag awgtwtgagt
                                                                            480
aaaaycagtt ttggtwaata ygtwaatatg tcmtaaataa acaakgcttt gacttatttc
                                                                            540
caaaaaaaa aaaaaaaa
                                                                            558
      <210> 182
      <211> 479
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (479)
      <223> n = A, T, C or G
      <400> 182
acagggwttk grggatgcta agsccccrga rwtygtttga tccaaccctg gcttwttttc
                                                                             60
agaggggaaa atggggccta gaagttacag mscatytagy tggtgcgmtg qcacccctqq
                                                                            120
cstcacacag astcccgagt agctgggact acaggcacac agtcactgaa gcaggccctg
                                                                            180
ttwgcaattc acgttgccac ctccaactta aacattcttc atatgtgatg tccttagtca
                                                                            240
ctaaggttaa actttcccac ccagaaaagg caacttagat aaaatcttag agtactttca tactmttcta agtcctcttc cagcctcact kkgagtcctm cytgggggtt gataggaant
                                                                            300
                                                                            360
ntctcttggc tttctcaata aartctctat ycatctcatg tttaatttgg tacgcatara
                                                                            420
awtgstgara aaattaaaat gttctggtty mactttaaaa araaaaaaaa aaaaaaaaa
                                                                            479
      <210> 183
      <211> 384
      <212> DNA
      <213> Homo sapien
      <400> 183
aggogggago agaagotaaa gocaaagooo aagaagagtg goagtgocag cactgqtqoo
                                                                             60
agtaccagta ccaataacag tgccagtgcc agtgccagca ccagtggtgg cttcagtgct
                                                                           120
ggtgccagcc tgaccgccac tctcacattt gggctcttcg ctggccttgg tggagctggt
                                                                           180
gccagcacca gtggcagete tggtgcctgt ggttteteet acaagtgaga ttttagatat tgttaateet gccagtettt etetteaage cagggtgcat ceteagaaac etaeteaaca
                                                                           240
                                                                           300
cagcactcta ggcagccact atcaatcaat tgaagttgac actctgcatt aratctattt
                                                                           360
gccatttcaa aaaaaaaaaa aaaa
                                                                           384
      <210> 184
      <211> 496
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(496)
      <223> n = A,T,C or G
      <400> 184
accgaattgg gaccgctggc ttataagcga tcatgtyynt ccrgtatkac ctcaacgagc
                                                                             60
agggagateg agtetataeg etgaagaaat ttgaceegat gggacaacaq acetgeteag
                                                                           120
cccatcctgc tcggttctcc ccagatgaca aatactctsg acaccgaatc accatcaaga
                                                                           180
aacgetteaa ggtgeteatg acceageaac egegeeetgt cetetgaggg tecettaaac
                                                                           240
tgatgtettt tetgeeacet gttaccecte ggagaeteeg taaccaaact etteggaetg
                                                                           300
```

```
tgagccctga tgcctttttg ccagccatac tctttggcat ccagtctctc gtggcgattg
                                                                          360
 attatgcttg tgtgaggcaa tcatggtggc atcacccata aagggaacac atttgacttt
                                                                          420
 tttttctcat attttaaatt actacmagaw tattwmagaw waaatgawtt gaaaaactst
                                                                          480
 taaaaaaaa aaaaaa
                                                                          496
       <210> 185
       <211> 384
       <212> DNA
       <213> Homo sapien
       <400> 185
gctggtagcc tatggcgkgg cccacggagg ggctcctgag gccacggrac agtgacttcc
                                                                           60
caaqtatcyt gcgcsgcgtc ttctaccgtc cctacctgca gatcttcggg cagattcccc
                                                                          120
aggaggacat ggacgtggcc ctcatggagc acagcaactg ytcgtcggag cccggcttct
                                                                          180
gggcacaccc teetggggcc caggegggca cetgegtete ceagtatgcc aactggetgg
                                                                          240
tagtactact cctcatcatc ttcctactca tagccaacat cctactagtc aacttactca
                                                                          300
ttgccatgtt cagttacaca ttcggcaaag tacagggcaa cagcgatctc tactgggaag
                                                                          360
gcgcagcgtt accgcctcat ccgg
                                                                          384
       <210> 186
       <211> 577
       <212> DNA
       <213> Homo sapien
      <220>
      <221> misc_feature
       <222> (1) ... (577)
      <223> n = A, T, C or G
      <400> 186
gagttagetc ctccacaacc ttgatgaggt cgtctgcagt ggcctctcgc ttcataccgc
                                                                           60
tnccatcgtc atactgtagg tttgccacca cytcctggca tcttggggcg gcntaatatt
                                                                          120
ccaggaaact ctcaatcaag tcaccgtcga tgaaacctgt gggctggttc tgtcttccgc
                                                                          180
teggtgtgaa aggateteee agaaggagtg etegatette eccacaettt tgatgaettt
                                                                          240
attgagtcga ttctgcatgt ccagcaggag gttgtaccag ctctctgaca gtgaggtcac
                                                                          300
cagccctatc atgccgttga mcgtgccgaa garcaccgag ccttgtgtgg gggkkgaagt
                                                                          360
ctcacccaga ttctgcatta ccagagagcc gtggcaaaag acattgacaa actcgcccag
                                                                          420
gtggaaaaag amcameteet ggargtgetn geegeteete gtemgttggt qqeaqeqetw
                                                                          480
tccttttgac acacaaacaa gttaaaggca ttttcagccc ccagaaantt gtcatcatcc
                                                                          540
aagatntcgc acagcactna tccagttggg attaaat
                                                                          577
      <210> 187
      <211> 534
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (534)
      <223> n = A, T, C or G
      <400> 187
aacatettee tgtataatge tgtgtaatat egateegatn ttgtetqstq aqaatyeatw
actkggaaaa gmaacattaa agcctggaca ctggtattaa aattcacaat atgcaacact
                                                                         120
ttaaacagtg tgtcaatctg ctcccyynac tttgtcatca ccagtctggg aakaaqqqta
                                                                         180
tgccctattc acacctgtta aaagggcgct aagcattttt gattcaacat ctttttttt gacacaagtc cgaaaaaagc aaaagtaaac agttatyaat ttgttagcca attcacttc
                                                                         240
                                                                          300
ttcatgggac agagccatyt gatttaaaaa gcaaattgca taatattgag cttygggagc
                                                                         360
tgatatttga gcggaagagt agcctttcta cttcaccaga cacaactccc tttcatattg
                                                                         420
ggatgttnac naaagtwatg tctctwacag atgggatgct tttgtggcaa ttctgttctg
                                                                         480
aggatetece agtttattta ceaettgeae aagaaggegt tttetteete agge
                                                                         534
```

```
<210> 188
      <211> 761
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(761)
      <223> n = A, T, C or G
      <400> 188
agaaaccagt atctctnaaa acaacctctc ataccttgtg gacctaattt tgtgtgcgtg
                                                                         60
tgtgtgtgcg cgcatattat ataqacaggc acatcttttt tacttttgta aaagcttatg
                                                                        120
                                                                       180
cctctttggt atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct
ttgtcttctg tgtaaatggt actagagaaa acacctatnt tatgagtcaa tctagttngt
                                                                       240
tttattcgac atgaaggaaa tttccagatn acaacactna caaactctcc ctkgackarg
                                                                        300
ggggacaaag aaaagcaaaa ctgamcataa raaacaatwa cctggtgaga arttgcataa
                                                                       360
acagaaatwr ggtagtatat tgaarnacag catcattaaa rmgttwtktt wttctccctt
                                                                       420
gcaaaaaaca tgtacngact tcccgttgag taatgccaag ttgtttttt tatnataaaa
                                                                        480
cttgcccttc attacatgtt tnaaagtggt gtggtgggcc aaaatattga aatgatggaa
                                                                       540
                                                                       600
ctgactgata aagctgtaca aataagcagt gtgcctaaca agcaacacag taatgttgac
atgettaatt cacaaatget aattteatta taaatgtttg etaaaataca etttgaacta
                                                                       660
                                                                       720
tttttctgtn ttcccagagc tgagatntta gattttatgt agtatnaagt gaaaaantac
gaaaataata acattgaaga aaaananaaa aaanaaaaaa a
                                                                       761
      <210> 189
      <211> 482
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(482)
      <223> n = A, T, C or G
      <400> 189
ttttttttt tttgccgatn ctactatttt attgcaggan gtggggggt atgcaccgca
                                                                         60
caccggggct atnagaagca agaaggaagg agggagggca cagccccttg ctgagcaaca
                                                                       120
aagecgeetg etgeettete tgtetgtete etggtgeagg cacatgggga gacetteece
                                                                       180
aaggcagggg ccaccagtcc aggggtggga atacaggggg tgggangtgt gcataagaag
                                                                       240
tgataggcac aggccacccg gtacagaccc ctcggctcct gacaggtnga tttcgaccag
                                                                       300
                                                                       360
gtcattgtgc cctgcccagg cacagcgtan atctggaaaa gacagaatgc tttccttttc
aaatttggct ngtcatngaa ngggcanttt tccaanttng gctnggtctt ggtacncttg
                                                                       420
gtteggeeca geteenegte caaaaantat teaccennet cenaattget tgenggneec
                                                                       480
                                                                       482
      <210> 190
      <211> 471
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(471)
      <223> n = A, T, C or G
      <400> 190
                                                                        60
ttttttttt ttttaaaaca gtttttcaca acaaaattta ttagaagaat agtggttttg
                                                                       120
aaaactctcg catccagtga gaactaccat acaccacatt acagctngga atgtnctcca
aatgtctggt caaatgatac aatggaacca ttcaatctta cacatgcacg aaagaacaag
                                                                       180
cqcttttqac atacaatgca caaaaaaaaa aggggggggg gaccacatgg attaaaattt
                                                                       240
taagtactca tcacatacat taagacacag ttctagtcca gtcnaaaatc agaactgcnt
                                                                       300
```

```
tgaaaaattt catgtatgca atccaaccaa agaacttnat tggtgatcat qantnctcta
                                                                        360
ctacatchac cttgatcatt gccaggaach aaaagtthaa ancachchgt acaaaaanaa
                                                                        420
tctgtaattn anttcaacct ccgtacngaa aaatnttnnt tatacactcc c
                                                                        471
       <210> 191
       <211> 402
       <212> DNA
       <213> Homo sapien
      <220>
      <221> misc_feature
       <222> (1) ... (402)
      <223> n = A,T,C or G
      <400> 191
gagggattga aggtctqttc tastqtcqqm ctqttcaqcc accaactcta acaagttgct
                                                                         60
gtottocact cactgtotgt aagottttta accoagaowg tatottoata aatagaacaa
                                                                        120
attetteace agteacatet tetaggacet ttttggatte agttagtata agetetteca
                                                                        180
cttcctttgt taagacttca tctggtaaag tcttaagttt tgtagaaagg aattyaattg
                                                                        240
ctcgttctct aacaatgtcc tctccttgaa gtatttggct gaacaaccca cctaaagtcc
                                                                        300
ctttgtgcat ccattttaaa tatacttaat agggcattgk tncactaggt taaattctgc
                                                                        360
aagagtcatc tgtctgcaaa agttgcgtta gtatatctgc ca
                                                                        402
      <210> 192
      <211> 601
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(601)
      <223> n = A, T, C or G
      <400> 192
gageteggat ecaataatet ttgtetgagg geageacaea tatneagtge eatggnaact
                                                                         60
ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac
                                                                        120
atgcytyttt gaytaccgtg tgccaagtgc tggtgattct yaacacacyt ccatcccgyt
                                                                        180
cttttgtgga aaaactggca cttktctgga actagcarga catcacttac aaattcaccc
                                                                        240
acgagacact tgaaaggtgt aacaaagcga ytcttgcatt gctttttgtc cctccggcac
                                                                        300
cagttgtcaa tactaacccg ctggtttgcc tccatcacat ttgtgatctg tagctctgga
                                                                        360
tacatotoot gacagtactg aagaacttot tottttgttt caaaagcaro tottggtgco
                                                                        420
tgttggatca ggttcccatt tcccagtcyg aatgttcaca tggcatattt wacttcccac
                                                                        480
aaaacattgc gatttgaggc tcagcaacag caaatcctgt tccggcattg gctgcaagag
                                                                        540
cctcgatgta gccggccagc gccaaggcag gcgccgtgag ccccaccagc agcagaagca
                                                                        600
                                                                        601
      <210> 193
      <211> 608
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(608)
      <223> n = A, T, C or G
      <400> 193
atacageeca nateceacea egaagatgeg ettgttgaet gagaacetga tgeggteact
                                                                         60
ggtcccgctg tagccccagc gactetecac ctgctggaag cggttgatgc tgcactcytt
                                                                        120
cccaacgcag gcagmagcgg gsccggtcaa tgaactccay tcgtggcttg gggtkgacgg
                                                                        180
tkaagtgcag gaagaggctg accacctcgc ggtccaccag gatgcccgac tgtgcgggac
                                                                        240
ctgcagcgaa actcctcgat ggtcatgagc gggaagcgaa tgaggcocag ggccttgccc
                                                                       300
```

agaaccttcc gcctgttctc tggcgtcacc gaccagcgga caaacggcrt tgaacagccg caggammgsc accagcgtgt ccaggtcaat ctgcagtgtt tttgtcgatg ttctccaggc gtcgcgcctg cgtgagcagc atgaaggcgt cacgcaat	cacctcacgg gtcggtgaag acaggctggc	atgcccagtg ccctccgcgg cagctgcggt	tgtcgcgctc gtratggcgt tcatcgaaga	360 420 480 540 600 608
<210> 194 <211> 392 <212> DNA <213> Homo sapien			100 mg	**
<220> <221> misc_feature <222> (1)(392) <223> n = A,T,C or G				
<pre>&lt;400&gt; 194 gaacggctgg accttgcctc gcattgtgct ccagtccgag cagccccaga ccgctgccgc tccgcctcaa tgcagaacca gtagtgggag tttgatttta cttgggaatt tcctctgtta aacaacaaca aaataacatg tttgcctgtt taaagaaaat attactgtta catatactgc aaataaatat agttattaaa ggttgtcant</pre>	ccgaagctaa cactgtgttt tatagctttt aagttgtata ttgcaatttc	gcctgcctct agagttaaga cccaatgcta aaagtaggtg	ggccttcccc gtgaacactg atttccaaac attctgtatt	60 120 180 240 300 360 392
<210> 195 <211> 502 <212> DNA <213> Homo sapien				
<220> <221> misc_feature <222> (1)(502) <223> n = A,T,C or G				
<400> 195  ccsttkgagg ggtkaggkyc cagttyccga ccgagctgag gcagatgttc ccacagtgac cctcncaagg aaagaccacs ttctggggac aagggaaggc cccattccgg ggstgttccc ccccasgagg aagaggccct gagtcctggg caaatgcaag ctcaccaagg tccctctca gscscacacc cacccagagc acgccacccg gcarcgtgga catctngtcc cagaaggggg gctnanaaaa aaaaanaaaa aa	ccccagagcc atgggctgga cgaggaggaa atcagacacc gtccccttcc ccatggggar	stgggstata gggcaggacc gggaaggggc ccttcacgtg stacaccctg tgtgctcaag	gtytctgacc tagaggcacc tctgtgtgcc tatccccaca amcggccact gartcgcngg	60 120 180 240 300 360 420 480 502
<210> 196 <211> 665 <212> DNA <213> Homo sapien				
<220> <221> misc_feature <222> (1)(665) <223> n = A,T,C or G				
<400> 196 ggttacttgg tttcattgcc accacttagt cctctggaag ccttgcgcag agcggacttt wagctgtttk gagttgatts gcaccactgc actwatttat tatcttgtga aaagtataac	gtaattgttg acccacaact	gagaataact tcaatatgaa	gctgaatttt aacyawttga	60 120 180 240

300

```
aagtatgatg aaaagcaawa gatatatat cttttattat gttaaattat gattgccatt
attaatcggc aaaatgtgga gtgtatgttc ttttcacagt aatatatgcc ttttgtaact
                                                                       360
tcacttggtt attttattgt aaatgartta caaaattctt aatttaagar aatggtatgt
                                                                       420
watatttatt tcattaattt ctttcctkgt ttacgtwaat tttgaaaaga wtgcatgatt
                                                                       480
                                                                       540
tettgacaga aategatett gatgetgtgg aagtagtttg acceacatee etatgagttt
                                                                       600
ttcttagaat gtataaaggt tgtagcccat cnaacttcaa agaaaaaaat gaccacatac
tttgcaatca ggctgaaatg tggcatgctn ttctaattcc aactttataa actagcaaan
                                                                       660
                                                                       665
aagtg
      <210> 197
      <211> 492
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(492)
      <223> n = A,T,C or G
      <400> 197
ttttntttt tttttttgc aggaaggatt ccatttattg tggatgcatt ttcacaatat
                                                                        60
atgtttattg gagcgatcca ttatcagtga aaagtatcaa gtgtttataa natttttagg
                                                                       120
aaggcagatt cacagaacat getngtenge ttgcagtttt acctegtana gatnacagag
                                                                       180
                                                                       240
aattatagtc naaccagtaa acnaggaatt tacttttcaa aagattaaat ccaaactgaa
caaaattcta ccctgaaact tactccatcc aaatattgga ataanagtca gcagtgatac
                                                                       300
attetettet gaactttaga ttttetagaa aaatatgtaa tagtgateag gaagagetet
                                                                       360
tgttcaaaag tacaacnaag caatgttccc ttaccatagg ccttaattca aactttgatc
                                                                       420
                                                                       480
cattleacte ceateacggg agteaatget acctgggaca ettgtatttt gtteatnetg
                                                                       492
ancntggctt aa
      <210> 198
      <211> 478
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(478)
      <223> n = A, T, C or G
      <400> 198
tttnttttgn atttcantct gtannaanta ttttcattat gtttattana aaaatatnaa
                                                                        60
                                                                       120
tgtntccacn acaaatcatn ttacntnagt aagaggccan ctacattgta caacatacac
                                                                       180
tgagtatatt ttgaaaagga caagtttaaa gtanacncat attgccganc atancacatt
                                                                       240
tatacatggc ttgattgata tttagcacag canaaactga gtgagttacc agaaanaaat
natatatgtc aatcngattt aagatacaaa acagatccta tggtacatan catcntgtag
                                                                       300
                                                                       360
gagttgtggc tttatgttta ctgaaagtca atgcagttcc tgtacaaaga gatggccgta
agcattctag tacctctact ccatggttaa gaatcgtaca cttatgttta catatgtnca
                                                                       420
                                                                       478
gggtaagaat tgtgttaagt naanttatgg agaggtccan gagaaaaatt tgatncaa
      <210> 199
      <211> 482
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(482)
      <223> n = A, T, C or G
      <400> 199
agtgacttgt cctccaacaa aaccccttga tcaagtttgt ggcactgaca atcagaccta
                                                                        60
```

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tgctagttcc tgtcatctat tcgctactaa atgcagactg gaggggacca aaaaggggca
                                                                     120
tcaactccag ctggattatt ttggagcctg caaatctatt cctacttgta cggactttga
                                                                     180
agtgattcag tttcctctac ggatgagaga ctggctcaag aatatcctca tgcagcttta
                                                                     240
                                                                     300
tgaaqccnac tctgaacacg ctggttatct nagatgagaa ncagagaaat aaagtcnaga
aaatttacct ggangaaaag aggetttngg etggggacca teecattgaa eettetetta
                                                                     360
anggacttta agaanaaact accacatgtn tgtngtatcc tggtgccngg ccgtttantg
                                                                     420
aachtngach neaccettht ggaatanant ettgaengen teetgaactt geteetetge
                                                                     480
                                                                     482
     <210> 200
      <211> 270
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(270)
      <223> n = A, T, C or G
      <400> 200
                                                                      60
eggeegeaag tgeaacteea getggggeeg tgeggaegaa gattetgeea geagttggte
                                                                     120
cgactgcgac gacggcggcg gcgacagtcg caggtgcagc gcgggcgcct ggggtcttgc
                                                                     180
aaggetgage tgacgecgea gaggtegtgt caegteecae gacettgaeg cegtegggga
                                                                     240
cagcoggaac agagcocggt gaangoggga ggcctcgggg agcccctcgg gaagggcggc
ccgagagata cgcaggtgca ggtggccgcc
                                                                     270
      <210> 201
      <211> 419
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (419)
      <223> n = A, T, C or G
      <400> 201
ttttttttt ttttggaatc tactgcgagc acagcaggtc agcaacaagt ttattttgca
                                                                      60
gctagcaagg taacagggta gggcatggtt acatgttcag gtcaacttcc tttgtcgtgg
                                                                     120
                                                                     180
ttgattggtt tgtctttatg ggggcggggt ggggtagggg aaancgaagc anaantaaca
tggagtgggt gcaccctccc tgtagaacct ggttacnaaa gcttggggca gttcacctgg
                                                                     240
totgtgaccg toattttctt gacatcaatg ttattagaag toaggatatc ttttagagag
                                                                     300
tccactgtnt ctggagggag attagggttt cttgccaana tccaancaaa atccacntga
                                                                     360
aaaagttgga tgatncangt acngaatacc ganggcatan ttctcatant cggtggcca
                                                                     419
      <210> 202
      <211> 509
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(509)
      <223> n = A, T, C or G
      <400> 202
60
tggcacttaa tccatttta tttcaaaatg tctacaaant ttnaatncnc cattatacng
                                                                     120
gtnattttnc aaaatctaaa nnttattcaa atntnagcca aantccttac ncaaatnnaa
                                                                     180
tacnoncaaa aatcaaaaat atacntntot ttoagcaaac ttngttacat aaattaaaaa
                                                                     240
aatatatacg gctggtgttt tcaaagtaca attatcttaa cactgcaaac atntttnnaa
                                                                     300
ggaactaaaa taaaaaaaaa cactnccgca aaggttaaag ggaacaacaa attcntttta
                                                                     360
```

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caacancnnc nattataaaa atcatatctc aaatcttagg ggaatatata cttcacacng
                                                                        420
 ggatcttaac ttttactnca ctttgtttat ttttttanaa ccattgtntt gggcccaaca
                                                                        480
 caatggnaat nccnccncnc tggactagt
                                                                        509
       <210> 203
       <211> 583
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(583)
      <223> n = A, T, C or G
      <400> 203
ttttttttt tttttttga cccccctctt ataaaaaaca agttaccatt ttattttact
                                                                         60
tacacatatt tattttataa ttggtattag atattcaaaa ggcagctttt aaaatcaaac
                                                                        120
taaatggaaa ctgccttaga tacataattc ttaggaatta gcttaaaatc tgcctaaagt
                                                                        180
gaaaatette tetagetett ttgactgtaa atttttgact ettgtaaaac atecaaatte
                                                                        240
atttttcttg tctttaaaat tatctaatct ttccattttt tccctattcc aagtcaattt
                                                                        300
gcttctctag cctcatttcc tagctcttat ctactattag taagtggctt ttttcctaaa
                                                                        360
agggaaaaca ggaagagana atggcacaca aaacaaacat tttatattca tatttctacc
                                                                        420
tacgttaata aaatagcatt ttgtgaagcc agctcaaaag aaggcttaga tccttttatg
                                                                        480
tccattttag tcactaaacg atatcnaaag tgccagaatg caaaaggttt gtgaacattt
                                                                        540
attcaaaagc taatataaga tatttcacat actcatcttt ctq
                                                                        583
      <210> 204
      <211> 589
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
     <222> (1) ... (589)
      <223> n = A, T, C or G
      <400> 204
ttttttttt tttttttt ttttttctc ttctttttt ttganaatga ggatcgagtt
                                                                         60
tttcactctc tagatagggc atgaagaaaa ctcatctttc cagctttaaa ataacaatca
                                                                       120
aatctcttat gctatatcat attttaagtt aaactaatga gtcactggct tatcttctcc
                                                                       180
tgaaggaaat ctgttcattc ttctcattca tatagttata tcaagtacta ccttgcatat
                                                                       240
tgagaggttt ttcttctcta tttacacata tatttccatg tgaatttgta tcaaaccttt
                                                                       300
attiticatgo aaactagaaa ataatginti cittigoata agagaagaga acaatainag
                                                                       360
cattacaaaa ctgctcaaat tgtttgttaa gnttatccat tataattagt tnggcaggag
                                                                       420
ctaatacaaa tcacatttac ngacnagcaa taataaaact gaagtaccag ttaaatatcc
                                                                       480
aaaataatta aaggaacatt tttagcctgg gtataattag ctaattcact ttacaagcat
                                                                       540
ttattnagaa tgaattcaca tgttattatt contagooca acacaatqq
                                                                       589
      <210> 205
      <211> 545
      <212> DNA
      <213> Homo sapien
     <220>
      <221> misc_feature
      <222> (1) ... (545)
      <223> n = A, T, C or G
     <400> 205
tttttntttt ttttttcagt aataatcaga acaatattta tttttatatt taaaattcat
                                                                        60
aqaaaagtgc cttacattta ataaaagttt gtttctcaaa gtgatcagag gaattagata
                                                                       120
tngtcttgaa caccaatatt aatttgagga aaatacacca aaatacatta agtaaattat
```

```
ttaagatcat agagettgta agtgaaaaga taaaatttga ceteagaaac tetgageatt
                                                                        240
aaaaatccac tattagcaaa taaattacta tggacttctt gctttaattt tgtgatgaat
                                                                        300
atggggtgtc actggtaaac caacacattc tgaaggatac attacttagt gatagattct
                                                                        360
tatgtacttt gctanatnac gtggatatga gttgacaagt ttctctttct tcaatctttt
                                                                        420
aaggggcnga ngaaatgagg aagaaaagaa aaggattacg catactgttc tttctatngg
                                                                        480
aaggattaga tatgtttoct ttgccaatat taaaaaaaata ataatgttta ctactagtga
                                                                        540
                                                                        545
aaccc
      <210> 206
      <211> 487
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(487)
      <223> n = A, T, C or G
      <400> 206
ttttttttt ttttttagtc aagtttctna tttttattat aattaaagtc ttggtcattt
                                                                         60
catttattaq ctctqcaact tacatattta aattaaagaa acgttnttag acaactgtna
                                                                        120
caatttataa atgtaaggtg ccattattga gtanatatat tcctccaaga gtggatgtgt
                                                                        180
cccttctccc accaactaat gaancagcaa cattagttta attttattag tagatnatac
                                                                        240
actgctgcaa acgctaattc tcttctccat ccccatgtng atattgtgta tatgtgtgag
                                                                        300
                                                                        360
ttggtnagaa tgcatcanca atctnacaat caacagcaag atgaagctag gcntgggctt
toggtgaaaa tagactgtgt ctgtctgaat caaatgatct gacctatoct cggtggcaag
                                                                        420
aactettega accepttect caaaggenge tgecacattt gtggentetn ttgeacttgt
                                                                        480
                                                                        487
ttcaaaa
      <210> 207
      <211> 332
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (332)
      <223> n = A, T, C or G
      <400> 207
tgaattggct aaaagactgc atttttanaa ctagcaactc ttatttcttt cctttaaaaa
                                                                        60
tacatagcat taaatcccaa atcctattta aagacctgac agcttgagaa ggtcactact
                                                                        120
                                                                        180
gcatttatag gaccttctgg tggttctgct gttacntttg aantctgaca atccttgana
atctttgcat gcagaggagg taaaaggtat tggattttca cagaggaana acacagcgca
                                                                        240
gaaatgaagg ggccaggctt actgagcttg tccactggag ggctcatggg tgggacatgg
                                                                        300
                                                                        332
aaaaqaaqqc aqcctaggcc ctggggagcc ca
      <210> 208
      <211> 524
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (524)
      <223> n = A, T, C or G
      <400> 208
agggcgtggt gcggagggcg ttactgtttt gtctcagtaa caataaatac aaaaagactg
                                                                         60
gttgtgttcc ggccccatcc aaccacgaag ttgatttctc ttgtgtgcag agtgactgat
                                                                        120
tttaaaggac atggagettg teacaatgte acaatgteac agtgtgaagg geacacteac
                                                                        180
tocogogtga ttoacattta gcaaccaaca atagotoatg agtocatact tgtaaatact
                                                                        240
```

```
tttggcagaa tacttnttga aacttgcaga, tgataactaa gatccaagat atttcccaaa
                                                                            300
 gtaaatagaa gtgggtcata atattaatta cctgttcaca tcagcttcca tttacaaqtc
                                                                            360
 atgageceag acactgaeat caaactaage ceaettagae tecteaceae cagtetgtee
                                                                             420
 tgtcatcaga caggaggctg tcaccttgac caaattctca ccagtcaatc atctatccaa
                                                                            480
 aaaccattac ctgatccact tccggtaatg caccaccttg gtga
                                                                            524
       <210> 209
       <211> 159
       <212> DNA
       <213> Homo sapien
       <400> 209
 gggtgaggaa atccagagtt gccatggaga aaattccagt gtcagcattc ttgctccttg
                                                                             60
 tggccctctc ctacactctg gccagagata ccacagtcaa acctggagcc aaaaaqqaca
                                                                            120
 caaaggactc tcgacccaaa ctgccccaga ccctctcca
                                                                            159
       <210> 210
       <211> 256
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1) ... (256)
       <223> n = A, T, C or G
       <400> 210
actocotggc agacaaaggc agaggagaga gototgttag ttotgtgttg ttgaactgcc
                                                                             60
actgaattte tttecaettg gactattaca tgccanttga gggactaatg gaaaaacgta tggggagatt ttanccaatt tangtntgta aatggggaga etggggeagg egggagagat
                                                                            120
                                                                            180
ttgcagggtg naaatgggan ggctggtttg ttanatgaac agggacatag gaggtaggca
                                                                            240
ccaggatgct aaatca
                                                                            256
       <210> 211
       <211> 264
       <212> DNA
       <213> Homo sapien
      <220>
       <221> misc_feature
       <222> (1)...(264)
       <223> n = A, T, C or G
       <400> 211
acattgtttt tttgagataa agcattgaga gagctctcct taacgtgaca caatggaagg
                                                                            60
actggaacac atacccacat ctttgttctg agggataatt ttctgataaa gtcttgctgt
                                                                           120
atattcaagc acatatgtta tatattattc agttccatgt ttatagccta gttaaggaga
                                                                           180
ggggagatac attcngaaag aggactgaaa gaaatactca agtnggaaaa cagaaaaaga
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      <213> Homo sapien
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cattacacat cqaaataaaa qaaaqqtqqc aqacttqccc aacgccaggc tgacatgtgc
                                                                            120
                                                                            180
tgcagggttg ttgtttttta attattattg ttagaaacgt cacccacagt ccctgttaat
ttgtatgtga cagccaactc tgagaaggtc ctatttttcc acctgcagag gatccagtct
                                                                            240
cactaggete etecttgece teacactgga gteteegeea gtgtgggtge ceactgacat
                                                                            300
      <210> 230
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 230
cagcagaaca aatacaaata tgaagagtgc aaagatctca taaaatctat gctgaggaat
                                                                             60
gagcgacagt tcaaggagga gaagcttgca gagcagctca agcaagctga ggagctcagg
                                                                            120
caatataaag teetggttea cacteaggaa egagagetga eecagttaag ggagaagttg
                                                                            180
cqqqaaqqqa qaqatqcctc cctctcattg aatgagcatc tccaggccct cctcactccg
                                                                            240
                                                                            300
qatqaaccqq acaaqtccca ggggcaggac ctccaagaaa cagacctcgg ccgcgaccac
                                                                            301
      <210> 231
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 231
gcaagcacgc tggcaaatct ctgtcaggtc agctccagag aagccattag tcattttagc
                                                                             60
caqqaactcc aagtccacat ccttggcaac tggggacttg cgcaggttag ccttgaggat
                                                                            120
ggcaacacgg gactteteat caggaagtgg gatgtagatg agetgateaa gacggccagg tetgaggatg geaggateaa tgatgteagg eeggttggta eegeeaatga tgaacacatt
                                                                            180
                                                                            240
tttttttgtg gacatgccat ccatttctgt caggatctgg ttgatgactc ggtcagcagc
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                                                                            301
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<210> 232

<211> 301

<212> DNA

<213> Homo sapien

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<400> 232
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ggcgacagcg gggcttcctg attctggaat ataactttgt gtaaattaac agccacctat
                                                                        120
agaagagtcc atctgctgtg aaggagagac agagaactct gggttccgtc gtcctgtcca
                                                                        180
cgtgctgtac caagtgctgg tgccagcctg ttacctgttc tcactgaaaa tctggctaat
                                                                        240
gctcttgtgt atcacttctg attctgacaa tcaatcaatc aatggcctag agcactgact
                                                                        300
       <210> 233
       <211> 301
       <212> DNA
       <213> Homo sapien
       <400> 233
atgactgact tcccagtaag gctctctaag gggtaagtag gaggatccac aggatttgag
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atgctaaggc cccagagatc gtttgatcca accctcttat tttcagaggg gaaaatgggg
                                                                        120
cctagaagtt acagagcatc tagctggtgc gctggcaccc ctggcctcac acagactccc
                                                                        180
gagtagctgg gactacaggc acacagtcac tgaagcaggc cctgttagca attctatgcg
                                                                        240
tacaaattaa catgagatga gtagagactt tattgagaaa gcaaqagaaa atcctatcaa
                                                                        300
                                                                        301
      <210> 234
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 234
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cattttattc atcatgatgc tttcttttgt ticttctttt cgttttcttc tttttcttit
                                                                        120
tcaatttcag caacatactt ctcaatttct tcaggattta aaatcttgag ggattgatct
                                                                        180
cgcctcatga cagcaagttc aatgtttttg ccacctgact gaaccacttc caggagtqcc
                                                                        240
ttgatcacca gcttaatggt cagatcatct gcttcaatgg cttcgtcagt atagttcttc
                                                                        300
                                                                        301
      <210> 235
      <211> 283
      <212> DNA
      <213> Homo sapien
      <400> 235
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                                                                         60
aatteeetea tettttaggg aateatttae eaggtttgga gaggatteag acageteagg
                                                                        120
tgctttcact aatgtctctg aacttctgtc cctctttgtt catggatagt ccaataaata
                                                                        180
atgttatett tgaactgatg etcataggag agaatataag aactetgagt gatateaaca
                                                                        240
ttagggattc aaagaaatat tagatttaag ctcacactgg tca
                                                                        283
      <210> 236
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 236
aggtcctcca ccaactgcct gaagcacggt taaaattggg aagaagtata gtgcagcata
                                                                        60
aatactttta aatcgatcag atttccctaa cccacatgca atcttcttca ccagaagagg
                                                                       120
teggageage atcattaata ecaageagaa tgegtaatag ataaatacaa tggtatatag
                                                                       180
tgggtagacg gcttcatgag tacagtgtac tgtggtatcg taatctggac ttgggttgta
                                                                       240
aagcatcgtg taccagtcag aaagcatcaa tactcgacat gaacgaatat aaagaacacc
                                                                       300
                                                                       301
      <210> 237
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<211> 301

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<212> DNA
      <213> Homo sapien
      <400> 237
cagtggtagt ggtggtggac gtggcgttgg tcgtggtgcc ttttttggtg cccgtcacaa
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actcaatttt tgttcqctcc tttttggcct tttccaattt gtccatctca attttctggg
                                                                       120
ccttqqctaa tqcctcataq taqqaqtcct cagaccagcc atggggatca aacatatcct
                                                                       180
                                                                       240
ttqqqtaqtt qqtqccaaqc tcqtcaatgg cacagaatgg atcagcttct cgtaaatcta
gggttccgaa attettett cetttggata atgtagttca tatccattce etcetttate
                                                                       300
                                                                       301
      <210> 238
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 238
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                                                                        60
gttcacagtt cageccetg ctcagaaaac caacgggeca gctaaggaga ggaggaggca
                                                                       120
cettgagact teeggagteg aggeteteea gggtteecea geceateaat cattttetge
                                                                       180
accccctgcc tgggaagcag ctccctgggg ggtgggaatg ggtgactaga agggatttca
                                                                       240
                                                                       300
qtqtqqqacc caqqqtctqt tcttcacagt aggaggtgga agggatgact aatttcttta
                                                                       301
      <210> 239
      <211> 239
      <212> DNA
      <213> Homo sapien
      <400> 239
ataagcagct agggaattet ttatttagta atgteetaac ataaaagtte acataactge
                                                                        60
                                                                       120
ttctgtcaaa ccatgatact gagctttgtg acaacccaga aataactaag agaaggcaaa
                                                                       180
cataatacct tagagatcaa gaaacattta cacagttcaa ctgtttaaaa atagctcaac
                                                                       239
attcagccag tgagtagagt gtgaatgcca gcatacacag tatacaggtc cttcaggga
      <210> 240
      <211> 300
      <212> DNA
      <213> Homo sapien
      <400> 240
                                                                        60
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gggatctgcc ctccagtgga accttttaag gaagaagtgg gcccaagcta agttccacat
                                                                       120
gctgggtgag ccagatgact tetgtteeet ggteacttte tteaatgggg cgaatggggg
                                                                       180
ctgccaggtt tttaaaatca tgcttcatct tgaagcacac ggtcacttca ccctcctcac
                                                                       240
gctgtgggtg tactttgatg aaaataccca ctttgttggc ctttctgaag ctataatgtc
                                                                       300
      <210> 241
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 241
qaqqtctqqt qctqaqqtct ctqqqctaqq aaqaqqaqtt ctqtqqaqct qgaaqccaqa
                                                                        60
                                                                       120
cctctttgga ggaaactcca gcagctatgt tggtgtctct gagggaatgc aacaaggctg
ctcctccatg tattggaaaa ctgcaaactg gactcaactg gaaggaagtg ctgctgccag
                                                                       180
tgtgaagaac cagcctgagg tgacagaaac ggaagcaaac aggaacagcc agtctttct
                                                                       240
tectectect greatacggt eteteteaag cateetttgt tgteagggge etaaaaggga
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                                                                       301
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<210> 242 <211> 301

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<212> DNA
       <213> Homo sapien
       <400> 242
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 tgtggcattt cctcattttc tacattgtag aatcaagagt gtaaataaat gtatatcgat
                                                                        120
 gtetteaaga atatateatt cettttteae tagaaceeat teaaaatata agteaagaat
                                                                        180
 cttaatatca acaaatatat caagcaaact ggaaggcaga ataactacca taatttagta
                                                                        240
 taagtaccca aagttttata aatcaaaagc cctaatgata accattttta qaattcaatc
                                                                        300
                                                                        301
       <210> 243
       <211> 301
       <212> DNA
       <213> Homo sapien
       <400> 243
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ggtggcccaa gctatgaaat cagagggagg cttcatctgg gcctgtaaaa actatgatgg
                                                                        120
tgacgtgcag tcggactctg tggcccaagg gtatggctct ctcggcatga tgaccagcgt
                                                                        180
gctggtttgt ccagatggca agacagtaga agcagaggct gcccacggga ctgtaacccg
                                                                        240
teactacege atgitecaga aaggacagga gacgiceace aateceatig ettecatiti
                                                                        300
                                                                        301
      <210> 244
      <211> 300
      <212> DNA
      <213> Homo sapien
      <400> 244
gctggtttgc aagaatgaaa tgaatgattc tacagctagg acttaacctt gaaatggaaa
                                                                         60
gtcatgcaat cccatttgca ggatctgtct gtgcacatgc ctctgtagag agcagcattc
                                                                        120
ccagggacct tggaaacagt tgacactgta aggtgcttgc tccccaagac acatcctaaa
                                                                        180
aggtgttgta atggtgaaaa cgtcttcctt ctttattgcc ccttcttatt tatgtgaaca
                                                                        240
actgtttgtc ttttgtgtat cttttttaaa ctgtaaagtt caattgtgaa aatgaatatc
                                                                        300
      <210> 245
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 245
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tatatactta gataaaaaat gaggtgaatt actatccatt gaaatcatgc tcttagaatt
                                                                       120
aaggccagga gatattgtca ttaatgtara cttcaggaca ctagagtata gcagccctat
                                                                       180
gttttcaaag agcagagatg caattaaata ttgtttagca tcaaaaaggc cactcaatac
                                                                       240
agctaataaa atgaaagacc taatttctaa agcaattctt tataatttac aaagttttaa
                                                                       300
                                                                       301
      <210> 246
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 246
ggtctgtcct acaatgcctg cttcttgaaa gaagtcggca ctttctagaa tagctaaata
                                                                        60
acctgggctt attttaaaga actatttgta gctcagattg gttttcctat ggctaaaata
                                                                       120
agtgcttctt gtgaaaatta aataaaacag ttaattcaaa gccttgatat atgttaccac
                                                                       180
taacaatcat actaaatata ttttgaagta caaagtttga catgctctaa agtgacaacc
                                                                       240
caaatgtgtc ttacaaaaca cgttcctaac aaggtatgct ttacactacc aatgcaqaaa
                                                                       300
                                                                       301
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<210> 247
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 247
aggteetttg geagggetea tggateagag eteaaactgg agggaaagge atttegggta
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qcctaaqaqq qcqactggcg gcaqcacaac caaggaaggc aaggttgttt cccccacgct
                                                                       120
qtqtcctqtq ttcaqqtqcq acacacaatc ctcatgggaa caggatcacc catqcqctqc
                                                                       180
ccttgatgat caaggttggg gcttaagtgg attaagggag gcaagttctg ggttccttgc
                                                                       240
cttttcaaac catgaagtca ggctctgtat ccctccttt cctaactgat attctaacta
                                                                       300
                                                                       301
      <210> 248
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 248
aggtccttgg agatgccatt tcagccgaag gactcttctw ttcggaagta caccctcact
                                                                        60
attaggaaga ttcttagggg taatttttct gaggaaggag aactagccaa cttaagaatt
                                                                       120
acaggaagaa agtggtttgg aagacagcca aagaaataaa agcagattaa attgtatcag
                                                                       180
qtacattcca gcctqttqqc aactccataa aaacatttca gattttaatc ccqaatttag
                                                                       240
ctaatgagac tggatttttg ttttttatgt tgtgtgtcgc agagctaaaa actcagttcc
                                                                       300
                                                                       301
      <210> 249
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 249
gtccagagga agcacctggt gctgaactag gcttgccctg ctgtgaactt gcacttggag
                                                                        60
ccctgacgct gctgttctcc ccgaaaaacc cgaccgacct ccgcgatctc cgtcccgccc
                                                                       120
ccagggagac acagcagtga ctcagagctg gtcgcacact gtgcctccct cctcaccgcc
                                                                       180
catcqtaatq aattatttq aaaattaatt ccaccatcct ttcaqattct qqatqqaaaq
                                                                       240
actgaatctt tgactcagaa ttgtttgctg aaaagaatga tgtgactttc ttagtcattt
                                                                       300
                                                                       301
      <210> 250
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 250
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cttatcttta ttggcttgat aaacataatt atttctaaca ctagcttatt tccagttgcc
                                                                       120
cataagcaca tcagtacttt tctctggctg gaatagtaaa ctaaagtatg gtacatctac
                                                                       180
ctaaaagact actatgtgga ataatacata ctaatgaagt attacatgat ttaaagacta
                                                                       240
caataaaacc aaacatgctt ataacattaa gaaaaacaat aaagatacat gattgaaacc
                                                                       300
                                                                       301
      <210> 251
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 251
qccqaqqtcc tacatttggc ccaqtttccc cctqcatcct ctccaqqqcc cctqcctcat
                                                                        60
agacaacctc atagagcata ggagaactgg ttgccctggg ggcaggggga ctgtctggat
                                                                       120
qqcaqqqqtc ctcaaaaatg ccactgtcac tgccaggaaa tgcttctgag cagtacacct
                                                                       180
cattgggatc aatgaaaagc ttcaagaaat cttcaggctc actctcttga aggcccggaa
                                                                       240
```

```
cctctggagg ggggcagtgg aatcccagct ccaggacgga tcctgtcgaa aagatatcct
                                                                              300
                                                                              301
       <210> 252
       <211> 301
       <212> DNA
       <213> Homo sapien
       <400> 252
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ttttctacat tgtagaatca agagtgtaaa taaatgtata tcgatgtctt caagaatata
                                                                              120
tcattccttt ttcactagga acccattcaa aatataagtc aagaatctta atatcaacaa
                                                                              180
atatatcaag caaactggaa ggcagaataa ctaccataat ttagtataag tacccaaagt
                                                                              240
tttataaatc aaaagcccta atgataacca tttttagaat tcaatcatca ctqtagaatc
                                                                              300
                                                                              301
       <210> 253
       <211> 301
       <212> DNA
       <213> Homo sapien
       <400> 253
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                                                                              60
caactaaaaa aaaaaaataa agaaaaaatg tgctgcgttc tgaaaaataa ctccttagct
                                                                              120
tggtctgatt gttttcagac cttaaaatat aaacttgttt cacaagcttt aatccatgtg
                                                                              180
gattttttt cttagagaac cacaaaacat aaaaggagca agtcggactg aatacctgtt
                                                                              240
tecatagtge ceacagggta tteeteacat tttetecata ggaaaatget tttteecaag
                                                                              300
                                                                              301
       <210> 254
       <211> 301
       <212> DNA
       <213> Homo sapien
       <400> 254
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                                                                              60
                                                                             120
                                                                             180
gaaaaaaata aagctttgga cttttcaagg ttgcttaaca ggtactgaaa gactggcctc
                                                                             240
acttaaactg agccaggaaa agctgcagat ttattaatgg gtgtgttagt gtgcagtgcc
                                                                             300
t
                                                                             301
      <210> 255
      <211> 302
      <212> DNA
      <213> Homo sapien
      <400> 255
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                                                                              60
attactgaaa tgtttctttt ctgaatataa atataaatat gtgcaaagtt tgacttggat
                                                                             120
tgggattttg ttgagttctt caagcatctc ctaataccct caagggcctg agtaggggg
                                                                             180
aggaaaaagg actggaggtg gaatctttat aaaaaacaag agtgattgag gcagattgta
                                                                             240
aacattatta aaaaacaaga aacaaacaaa aaaatagaga aaaaaaccac cccaacacac
                                                                             300
                                                                             302
      <210> 256
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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<222> (1)...(301)
      <223> n = A, T, C or G
      <400> 256
gttccagaaa acattgaagg tggcttccca aagtctaact agggataccc cctctagcct
                                                                         60
aggaccetee tecceacace teaatecace aaaccateca taatgeacee agataggeee
                                                                        120
acceccaaaa geetggacae ettgageaea eagttatgae eaggacagae teatetetat
                                                                        180
aggcaaatag ctgctggcaa actggcatta cctggtttgt ggggatgggg gggcaagtgt
                                                                        240
qtqqcctctc qqcctqqtta qcaaqaacat tcagggtagg cctaagttan tcgtgttagt
                                                                        300
                                                                        301
      <210> 257
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 257
gttgtggagg aactetgget tgctcattaa gtcctactga ttttcactat cccctgaatt
                                                                        60
tececactta tttttqtett teaetatege aggeettaga agaggtetae etgeeteeag
                                                                        120
tettacetag tecagtetae eeeetggagt tagaatggee ateetgaagt gaaaagtaat
                                                                        180
gtcacattac tcccttcagt gatttcttgt agaagtgcca atccctgaat gccaccaaga
                                                                        240
tettaatett cacatettta atettatete tttgacteet etttacaceg gagaaggete
                                                                        300
                                                                        301
      <210> 258
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(301)
      <223> n = A, T, C or G
      <400> 258
cagcagtagt agatgccgta tgccagcacg cccagcactc ccaggatcag caccagcacc
                                                                        60
aggggccag ccaccaggcg cagaagcaag ataaacagta ggctcaagac cagagccacc
                                                                        120
cccagggcaa caagaatcca ataccaggac tgggcaaaat cttcaaagat cttaacactg
                                                                        180
atgtctcggg cattgaggct gtcaataana cgctgatccc ctgctgtatg gtggtgtcat
                                                                        240
                                                                        300
tgqtqatccc tgggagcgcc ggtggagtaa cgttggtcca tggaaagcag cgcccacaac
                                                                        301
      <210> 259
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(301)
      <223> n = A, T, C or G
      <400> 259
                                                                        60
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gtgtcctgaa gtgatttgga cccctgaggg cagacaccta agtaggaatc ccaqtgggaa
                                                                        120
                                                                        180
qcaaaqccat aaqqaaqccc aggattcctt gtgatcagga agtgggccag gaaggtctgt
tocageteae ateteatetg catgeageae ggaceggatg egeceaetgg gtettggett
                                                                        240
coctcocate tteteaagea gtgteettgt tgagecattt geateettgg etceaggtgg
                                                                        300
                                                                        301
```

<210> 260 <211> 301

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<212> DNA
       <213> Homo sapien
       <400> 260
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                                                                         60
 aaggtgtctt aacttgaaaa agattaggag tcactggttt acaagttata attgaatgaa
                                                                        120
 agaactgtaa cagccacagt tggccatttc atgccaatgg cagcaaacaa caggattaac
                                                                        180
 tagggcaaaa taaataagtg tgtggaagcc ctgataagtg cttaataaac agactgattc
                                                                        240
 actgagacat cagtacetge eegggeggee getegageeg aattetgeag atatecatea
                                                                        300
                                                                        301
       <210> 261
       <211> 301
       <212> DNA
       <213> Homo sapien
       <400> 261
aaatattcga gcaaatcctg taactaatgt gtctccataa aaggctttga actcagtgaa
                                                                         60
totgottoca tocacgatto tagoaatgac ototoggaca toaaagotoo tottaaggtt
                                                                        120
agcaccaact attocataca attoatcago aggaaataaa ggotottoag aaggttoaat
                                                                        180
qqtgacatcc aatttcttct gataatttag attcctcaca accttcctag ttaagtgaag
                                                                        240
ggcatgatga tcatccaaag cccagtggtc acttactcca gactttctqc aatqaaqatc
                                                                        300
                                                                        301
      <210> 262
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 262
gaggagagcc tgttacagca tttgtaagca cagaatactc caggagtatt tgtaattgtc
                                                                         60
tgtgagcttc ttgccgcaag tctctcagaa atttaaaaag atgcaaatcc ctgagtcacc
                                                                        120
cctagacttc ctaaaccaga tectetgggg ctggaacctg gcactetgca tttgtaatga
                                                                        180
gggctttctg gtgcacacct aattttgtgc atctttgccc taaatcctgg attagtgccc
                                                                        240
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C
                                                                        301
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      <400> 263
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aaaattacta cttaatccta attcacaata acaatggcat taaqqtttqa cttgaqttqq
                                                                        120
ttcttagtat tatttatggt aaataggctc ttaccacttg caaataactg gccacatcat
                                                                        180
taatgactga cttcccagta aggctctcta aggggtaagt angaggatcc acaggatttg
                                                                       240
agatgctaag gccccagaga tcgtttgatc caaccctctt attttcagag gggaaaatgg
                                                                       300
                                                                        301
      <210> 264
      <211> 301
      <212> DNA
      <213> Homo sapien
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aatgaatgac tctaaaaaca gtggatagat ctagaattgt ctcaattata gatgcaaagt acccttcata taaattcact a	aacattttaa tataactaaa	gaaaaccata ctactatagt	scatttgaca agtaaagaaa	gatgagaaag tacatttcac	120 180 240 300 301
<210> 265 <211> 301 <212> DNA <213> Homo sapi	en			en e	
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<210> 266 <211> 301 <212> DNA <213> Homo sapi	en				
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<210> 267 <211> 301 <212> DNA <213> Homo sapi	en				
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<210> 268 <211> 301 <212> DNA <213> Homo sapi	en				
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					301

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<400> 269
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aaaattacct ttattcacac atctcaaaac aattctgcaa attcttagtg aagtttaact
                                                                        120
ataqtcacag accttaaata ttcacattgt tttctatgtc tactgaaaat aagttcacta
                                                                        180
                                                                        240
cttttctgga tattctttac aaaatcttat taaaattcct ggtattatca cccccaatta
tacagtagca caaccacctt atgtagtttt tacatgatag ctctgtagaa gtttcacatc
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                                                                        301
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      <211> 301
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      <400> 270
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cacaaqaata catatteett ttatttetaa ggagttaaac atagatgtag etgatgtgga
gagettgetg gtgcagtgca tattggataa cactattcat ggccgaattg atcaagtcaa
                                                                        180
                                                                        240
ccaactcctt qaactggatc atcagaagaa gggtggtgca cgatatactg cactagataa
tggaccaacc aactaaattc tctcaccagg ctgtatcagt aaactggctt aacagaaaac
                                                                        300
                                                                        301
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      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
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tttatagete atetttaggg ttgatattca gttcatgett ceettgetgt tettgateca
                                                                        120
gaattgcaat cacttcatca gcctgtattc gctccaattc tctataaagt gggtccaagg
                                                                        180
                                                                        240
tgaaccacag agccacagca cacctctttc ccttggtgac tgccttcacc ccatganggt
tetetectee agatganaac tgateatgeg eccacatttt gggttttata gaageagtea
                                                                        300
                                                                        301
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      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 272
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                                                                         60
ttatcagaaa accaaatgag cctggaatct tcataatacc taaacatgcc gtatttagga
                                                                        120
tccaataatt ccctcatgat gagcaagaaa aattctttgc gcacccctcc tgcatccaca
                                                                        180
                                                                        240
gcatcttctc caacaaatat aaccttgagt ggcttcttgt aatctatgtt ctttgttttc
                                                                        300
ctaaggactt ccattgcatc tcctacaata ttttctctac gcaccactag aattaagcag
                                                                        301
      <210> 273
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(301)
      \langle 223 \rangle n = A, T, C or G
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<210> 274 <211> 301 <212> DNA <213> Homo sapid	en				
<220> <221> misc_feat 222 (1)(30) <223> n = A,T,C	1) .				
<400> 274 cttatatact ctttctcaga aacagtaaat gattattaga tgattctctt tggaatctga tctaggtatg gttgcattct aattgtgctt cttttgataa c	gagaangaat atgagatcaa cgtcttcttt	ggaccaagga gaggccagct tctgcagtag	gacagaaatt ttagcttgtg ataatgaggt	aacttgtaaa gaaaagtcca aaccgaaggc	60 120 180 240 300 301
<210> 275 <211> 301 <212> DNA <213> Homo sapi	en .				
<220> <221> misc_feat <222> (1)(30) <223> n = A,T,C	1)				
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<210> 276 <211> 301 <212> DNA <213> Homo sapid	en				
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<210> 277 <211> 301 <212> DNA <213> Homo sapi	en				

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<220>
       <221> misc feature
       <222> (1)...(301)
       <223> n = A, T, C or G
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                                                                            60
atacagagga cttggaggaa gcagagcaac tgaatttaat ttaaaagaag gaaaacattg
                                                                           120
quatcatggc actectgata ettteccaaa teaacactet caatgeecca cectegteet
                                                                           180
caccatagtg gggagactaa agtggccacg gatttgcctt angtgtgcag tgcgttctga
                                                                           240
gttenetgte gattacatet gaccagtete ettttteega agteenteeg tteaatettg
                                                                           300
                                                                           301
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       <211> 301
       <212> DNA
       <213> Homo sapien
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       <221> misc feature
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aacatatcaa atgaaacagg gaaaatgaag ctgacaattt atggaagcca gggcttgtca
                                                                           120
cagtetetae tgitattatg cattacetgg gaatttatat aageeettaa taataatgee aatgaacate teatgtgtge teacaatgtt etggeactat tataagtget teacaggttt
                                                                           180
                                                                           240
tatgtgttct tcgtaacttt atggantagg tactcggccg cgaacacgct aagccgaatt
                                                                           300
                                                                           301
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      <211> 301
      <212> DNA
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      <222> (1) ... (301)
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gttatattaa ttgccaatat aagtaaatat agattatata tgtatagtgt ttcacaaagc
                                                                           120
ttagacettt acetteeage caccecacag tgettgatat tteagagtea gteattggtt
                                                                           180
atacatgtgt agttccaaag cacataagct agaanaanaa atatttctag ggagcactac
                                                                           240
catctgtttt cacatgaaat gccacacaca tagaactcca acatcaattt cattgcacag
                                                                           300
                                                                           301
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      <211> 301
      <212> DNA
      <213> Homo sapien
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                                                                            60
tagaaaggtg gtggaaccaa attgtggtca atggaaatag gagaatatgg ttctcactct
                                                                           120
tgagaaaaaa acctaagatt agcccaggta gttgcctgta acttcagttt ttctgcctgg
                                                                           180
gtttgatata gtttagggtt ggggttagat taagatctaa attacatcag gacaaagaga
                                                                           240
cagactatta actocacagt taattaagga ggtatgttoc atgtttattt gttaaagcag
                                                                           300
t
                                                                           301
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                                                                       120
                                                                       180
atqtqqtaqc aatqqcttta tcqqqttata cqqatqaqaa qaactccctt tqqaqaqaaa
tqtqtagcac actgcgatta cagctaaata acccgtattt gtgtgtcatg tttgcatttc
                                                                       240
tgacaagtga aacaggatct tacgatggag ttttgtatga aaacaaagtt gcagtacctc
                                                                       300
                                                                       301
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      <211> 301
      <212> DNA
      <213> Homo sapien
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tocaquacco aaaaattaag aaattcaaaa agacattttg tgggcacctg ctagcacaga
                                                                       120
agegeagaag caaageeeag geagaaceat getaacetta cageteagee tgeacagaag
                                                                       180
cgcagaagca aagcccaggc agaaccatgc taaccttaca gctcagcctg cacagaagcg
                                                                       240
cagaagcaaa geccaggeag aacatgetaa cettacaget cageetgeac agaagcacag
                                                                       300
                                                                       301
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      <212> DNA
      <213> Homo sapien
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cactttgagg gctttataat aatatgctgc ttgaaaaaaa aaatgtgtag ttgatactca
                                                                       120
qtqcatctcc agacatagta aggggttgct ctgaccaatc aggtgatcat tttttctatc
                                                                       180
acttoccagg tittatgcaa aaattitgti aaattotata atggigatat goatottita
                                                                       240
ggaaacatat acatttttaa aaatctattt tatgtaagaa ctgacagacg aatttgcttt
                                                                       300
                                                                       301
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      <211> 301
      <212> DNA
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                                                                        60
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gcttcgtgtg tgggcaaagc aacatcttcc ctaaatatat attaccaaga aaagcaagaa
                                                                       120
gcagattagg tttttgacaa aacaaacagg ccaaaagggg gctgacctgg agcagagcat
                                                                       180
ggtgagaggc aaggcatgag agggcaagtt tgttgtggac agatctgtgc ctactttatt
                                                                       240
                                                                       300
actggagtaa aagaaaacaa agttcattga tgtcgaagga tatatacagt gttagaaatt
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                                                                        120
 caggaaagca aatgctattt acagacctgc aagccctccc tcaaacnaaa ctatttctgg
                                                                        180
 attaaatatg totgacttot tttgaggtoa cacgactagg caaatgctat ttacgatotg
                                                                        240
 caaaagctgt ttgaagagtc aaagccccca tgtgaacacg atttctggac cctgtaacag
                                                                        300
                                                                        301
       <210> 286
       <211> 301
       <212> DNA
       <213> Homo sapien
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tgtatattat ttttgcctta cagtggatca ttctagtagg aaaggacagt aagattttt
                                                                        120
atcaaaatgt gtcatgccag taagagatgt tatattcttt tctcatttct tccccaccca
                                                                        180
adaataagct accatatagc ttataagtct caaatttttg ccttttacta aaatgtgatt
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gtttctgttc attgtgtatg cttcatcacc tatattaggc aaattccatt ttttcccttg
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                                                                        301
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      <211> 301
      <212> DNA
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cccagaagga acgtagagat cagatattac aacagctttg ttttgagggt tagaaatatg
                                                                        120
aaatgatttg gttatgaacg cacagtttag gcagcagggc cagaatcctg accetetgee
                                                                        180
cogtogttat ctcctcccca gcttggctgc ctcatgttat cacagtattc cattttgttt
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gttgcatgtc ttgtgaagcc atcaagattt tctcgtctgt tttcctctca ttggtaatgc
                                                                        300
t
                                                                        301
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      <211> 301
      <212> DNA
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agtcaatagg aagacaaatt ccagttccag ctcagtctgg gtatctgcaa agctgcaaaa
                                                                        120
gatetttaaa gacaatttea agagaatatt teettaaagt tggcaatttg gagateatae
                                                                        180
aaaagcatct gcttttgtga tttaatttag ctcatctggc cactggaaga atccaaacag
                                                                        240
tctgccttaa ttttggatga atgcatgatg gaaattcaat aatttagaaa gttaaaaaaa
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                                                                        301
      <210> 289
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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      <223> n = A, T, C or G
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                                                                         60
gcttttgatg tctccaagta gtccaccttc atttaactct ttgaaactgt atcatctttg
                                                                       120
ccaagtaaga gtggtggcct atttcagctg ctttgacaaa atgactggct cctgacttaa
                                                                       180
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cgttctataa atgaatgtgc tgaagcaaag tgtgttttgt tttggactct ctgtggtccc a				240 300 301
<210> 290 <211> 301 <212> DNA <213> Homo sapien				
<220> <221> misc_feature <222> (1)(301) <223> n = A,T,C or G				• •
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<210> 291 <211> 301 <212> DNA <213> Homo sapien				
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<210> 292 <211> 301 <212> DNA <213> Homo sapien				
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<210> 293 <211> 301 <212> DNA <213> Homo sapien				
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gtgagaattt tttaaaaggc tacttgtata ataaccettg teatttttaa tgtacetegg
                                                                      240
 ecgegaceae getaageega attetgeaga tateeateae actggeggee getegageat
                                                                      300
                                                                      301
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      <211> 301
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      <221> misc_feature
      <222> (1)...(301)
      <223> n = A, T, C \text{ or } G
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                                                                      120
tttaactata gtcacaganc ttaaatattc acattgtttt ctatgtctac tqaaaataaq
                                                                      180
ttcactactt ttctgggata ttctttacaa aatcttatta aaattcctgg tattatcacc
                                                                      240
cccaattata cagtagcaca accaccttat gtagttttta catgatagct ctgtagaggt
                                                                      300
t
                                                                      301
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      <211> 305
      <212> DNA
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                                                                      180
actggtagaa aaacrtetga agagetagte tateageate tgacaggtga attggatggt.
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tctct
                                                                      305
      <210> 296
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 296
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                                                                       60
cacctagtag taaactaaaa ataaactgaa actttatgga atctgaagtt attttccttg
                                                                     120
attaaataga attaataaac caatatgagg aaacatgaaa ccatgcaatc tactatcaac
                                                                     180
tttgaaaaag tgattgaacg aaccacttag ctttcagatg atgaacactg ataagtcatt
                                                                      240
tgtcattact ataaatttta aaatctgtta ataagatggc ctatagggag gaaaaagggg
                                                                     300
                                                                     301
C
      <210> 297
      <211> 300
      <212> DNA °
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(300)
      <223> n = A, T, C or G
      <400> 297
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                                                                      60
aaggttttga aaaccttgaa ggagaatcat tttgacaaga agtacttaag agtctagaga
                                                                     120
acaaagangt gaaccagctg aaagctctcg ggggaanctt acatgtgttg ttaggcctgt
                                                                     180
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tocatcattg ggagtgcact ggccatccct caaaatttgt ctgggctggc ctgagtgaccgcacctc ggccgcgacc acgctaagcc gaattctgca gatatccatc acactgg	
accidences adaption and contract and account account and account and account and account account and account account account and account and account and account account and account account account and account account account account and account account account account and account accou	-gg 500
<210> 298	
<211> 301	
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<213> Homo sapien	
<220>	<i>∀</i> ,±
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<222> (1)(301)	£ 1
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tgggattgca ggctcacgcc accataccca gctaattttt ttgtattttt agtagag	acg 180
gagtttegec atgttggeca getggtetea aacteetgae eteaagegae etgeetg	cet 240
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ccacatcatt aatgactgac ttcccagtaa ggctctctaa ggggtaagta ggaggatcca
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Val Leu Gly Trp Val Ala Glu Leu
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                                                                       420
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                                                                       540
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gttcaatyaa aaagacactt ancccatgtg g
                                                                            151
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      <221> misc_feature
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                                                                            120
agagttacta cgaatcccat cttggttcca gctatatcac tgacagcatg gtagaagact
                                                                            180
gcgaacetea ettetagaet tteacggtgg gacgaaacgg gtteagaaac tgccagggge etcatacagg gatateaaaa taccetttgt getacecagg ceetggggaa teaggtgaet
                                                                            240
                                                                            300
cacacaaatg caatagttgg tcactgcatt tttacctgaa ccaaagctaa acccggtgtt
                                                                            360
qccaccatqc accatggcat gccagagttc aacactgttg ctcttgaaaa ttgggtctga
                                                                            420
aaaaacgcac aagagcccct gccctgccct agctgangca c
                                                                            461
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aqtaaqaqtq qtqqcctatt tcaqctqctt tqacaaaatq actqqctcct qacttaacqt
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totataaatg aatgtgotga agcaaagtgo coatggtggo ggogaagaag agaaagatgt
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                                                                           120
gaactectae accateggge tgggeetgea cagtettgag geegaecaag ageeagggag ceagatggtg gaggeeagee teteegtaeg geaeceagag tacaacagae cettgetege
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                                                                            240
                                                                            300
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catcagcatt gcttcgcagt gccctaccgc ggggaactct tgcctcgttt ctggctgggg
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totqctqqcq aacqqcaqaa tqcctaccqt qctqcaqtqc qtqaacqtqt cqqtqqtqtc
                                                                            420
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840

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				cccc															960
				actc														1	020
	ggt	ccca	gcc	cctc	ctcc	ct c	agac	ccag	c gg	tcca	atgc	cac	ctag	act	ctcc	ctgt	ac.		080
				cttg															.140
				gatc	-	aa t	aaag	tcta	a ga	gaag	cgca	aaa	aaaa	aaa	aaaa	aaaa	aa		.200
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				220															
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		<	213>	Home	o sa	pien													
		_	4005	227															
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	1		0,10	~~-	5					10		*****		DCG	15	1100			
	Glu	Asn	Glu	Leu	Phe	Cys	Ser	Gly	Val	Leu	Val	His	Pro	Gln	Trp	Val			
				20		_			25		_		_	30				200	
	Leu	Ser		Ala	His	Cys	Phe		Asn	Ser	Tyr	Thr		Gly	Leu	Gly			
	T eu	ије	35 Ser	Leu	<i>(</i> 21)	λla	Δen	40 Gln	Gla	Dro	G1 v	Sar	45 Gln	Mot	Val	Clu			
	neu	50	Ser	ъси	Giu	та	55	GIII	GIU	110	GLY	60	GIII	Met	Val	Gra			
	Ala	Ser	Leu	Ser	Val	Arg	His	Pro	Glu	Tyr	Asn	Arg	Pro	Leu	Leu	Ala			
	65					70					75	_				80			
	Asn	Asp	Leu	Met		Ile	Lys	Leu	Asp		Ser	Val	Ser	Glu		Asp	12.3		
	Thr.	Tlo		50=	·85	Sor	Tlo	712	C~~	90	C	Dwo	πh ~	71.	95	N			200
	TIII	116	ALG	Ser 100	116	Ser	116	MIG	105	GIII	Cys	PLO	THE	110		ASII		-14	
	Ser	Cys	Leu	Val	Ser	Gly	Trp	Gly		Leu	Ala	Asn	Gly			Pro			
		-	115			,	-	120					125						
	Thr.		Leu	Gln	Cys	Val		Val	Ser	Val	Val		Glu	Glu	Val	Cys			
	Com	130	7 011	W	7.00	Dma	135	<b>M</b>	114 -	Dwa	C	140	nh -	C	7.1 a	<b>61</b>			
	145	гуѕ	ren	Tyr	Asp	150	ьеи	Tyr	HIS	Pro	155	met	Pne	Cys	ATS	160			
		Glv	Gln	Asp	Gln		Asp	Ser	Cvs	Asn		Asp	Ser	Glv	Glv				
					165					170				-	175				
	Leu	Ile	Cys	Asn	Gly	Tyr	Leu	Gln		Leu	Val	Ser	Phe			Ala	1.7		
	D===	C	C1	180	17.5 1	C1	37 m 1	Dwa	185	171	m		n	190		T	÷	1 1 1 1 1 1	* *
	PLO	Cys	195	Gln	Val	GIA	val	200	GIÀ	vai	ıyı	Inr	205	Leu	cys	ràs			
- 3	Phe	Thr		Trp	Ile	Glu	Lvs		Val	Gln	Ala	Ser							
		210		•			215	٠,				220						132	
														,		:			
			210>												. 30				
			211>	DNA															
		_		Homo		oien									•				
		_									-								٠.
			100>														· • .		
				ggta															60
				jgcgg jgtgc															120 180
				cttg												lgecg	g	_	234
	,	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	~~ 9 `	9	-336	- 90				,,,,,,,,		39	3-35	,~9 !	a			•	,,,,
		<2	10>	329											٠.				
			11>								7.4							٠.	
			12>																
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	Leu			Gly	Ser	Cys	Ser	Gln	Ile	Ile	Asn	Gly	Glu	Asp	Cys	Ser	٠.,		
	1				5					10		-		-	15				: .

```
Pro His Ser Gln Pro Trp Gln Ala Ala Leu Val Met Glu Asn Glu Leu
           ~ 20
                                  25
Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val Leu Ser Ala Thr
His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu
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qtacatcaac tgttcagctt cctgggaaag tagttgtggt cacaggagct aatacaggta
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gettettage tgaggaaaag cacetecaeg ttttgateaa caatgeagga gtgatgatgt
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gtccgtactc gaagacagca gatggctttg agatgcacat aggagtcaac cacttgggtc
                                                                           480
acttectect acceptetg etgetagaga actaaagga atcageecca teaaggatag
                                                                           540
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                                                                           660
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                                                                           780
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teteetttt catcaagaet eeteageagg gageecagae eageetgeae tgtgeettaa
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cagaaggtct tgagattcta agtgggaatc atttcagtga ctgtcatgtg gcatgggtct
                                                                           900
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                                                                          1080
                                                                          1140
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                                                                          1260
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                                                                          1380
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                                                                          1440
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                                                                          1560
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                                                                      1740
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                                                                      1920
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                                                                      2160
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                                                                      2280
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                                                                      2340
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                                                                      2400
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                                                                      2460
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      <211> 3030
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<212> DNA

<213> Homo sapien

<400> 333

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<210> 334 <211> 2417 <212> DNA <213> Homo sapien

#### <400> 334

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<213> Homo sapien
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eccgagetge etteteceae acteaggtga tegagttgga gaggaagtte agecateaga
                                                                        180
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# 105 ·

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<213> Homo sapien

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 Ala
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 Ser
 Asp
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## <213> Homo sapien

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	•		900					905	Leu				910	-	
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945	•	_		_	950				Gln	955			_		·960
Asn	Glu	GLu	Tyr	H1S	Ser	Asp	Glu	GIn	Asn	Asp	Thr	GIn	гля	Gln	Phe

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	1425				Leu	1430	)				1435	,	_		_	144
					Gln 1445	i				1450	}				1455	•
1	⊔yŏ	nsp	$ar\lambda$	usb	Arg	<b>∵</b> ⊥u	AaT	GTU	GIU	GTU	rie c	ьys	∟ys	пlS	CILL	oer

Asn Asn Val Gly Leu Leu Glu Asn Leu Thr Asn Gly Val Thr Ala Gly 1475 . 1480 Asn Gly Asp Asn Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu . 1495 Asn Gln Gln Phe Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Glu Gly Ser Glu Asn Gly Gln Pro Glu Lys Arg Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Leu Glu Asn Phe Met Ala Ile Glu Glu Met Lys Lys His Gly Ser Thr His Val Gly Phe Pro Glu Asn Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Asp Gly Leu Ile Pro Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu Asn Glu Glu Tyr His Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile Leu Ile His Glu Glu Lys Gln Ile Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser Leu Ser Cys Lys Lys Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu Arg Glu Glu Ile Ala Met Leu Arg Leu Glu Leu Asp Thr Met Lys His Gln Ser Gln Leu 

<210> 379 <211> 656 <212> PRT

<213> Homo sapien

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Leu His Leu Ala Ser Ala Asn Gly Asn Ser Glu Val Val Lys Leu Leu Leu Asp Arg Arg Cys Gln Leu Asn Val Leu Asp Asn Lys Lys Arg Thr Ala Leu Ile Lys Ala Val Gln Cys Gln Glu Asp Glu Cys Ala Leu Met Leu Leu Glu His Gly Thr Asp Pro Asn Ile Pro Asp Glu Tyr Gly Asn Thr Thr Leu His Tyr Ala Ile Tyr Asn Glu Asp Lys Leu Met Ala Lys Ala Leu Leu Leu Tyr Gly Ala Asp Ile Glu Ser Lys Asn Lys His Gly Leu Thr Pro Leu Leu Gly Val His Glu Gln Lys Gln Gln Val Val Lys Phe Leu Ile Lys Lys Lys Ala Asn Leu Asn Ala Leu Asp Arg Tyr Gly Arg Thr Ala Leu Ile Leu Ala Val Cys Cys Gly Ser Ala Ser Ile Val Ser Leu Leu Glu Gln Asn Ile Asp Val Ser Ser Gln Asp Leu Ser Gly Gln Thr Ala Arg Glu Tyr Ala Val Ser Ser His His His Val Ile Cys Gln Leu Leu Ser Asp Tyr Lys Glu Lys Gln Met Leu Lys Ile Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Phe Lys Gly Ser Glu Asn Ser Gln Pro Glu Lys Met Ser Gln Glu Pro Glu Ile Asn Lys Asp Gly Asp Arg Glu Val Glu Glu Glu Met Lys Lys His Glu Ser Asn Asn Val Gly Leu Leu Glu Asn Leu Thr Asn Gly Val Thr Ala Gly Asn Gly Asn Gly Leu Ile Pro Gln Arg Lys Ser Arg Thr Pro Glu Asn Gln Gln Phe Pro Asp Asn Glu Ser Glu Glu Tyr His Arg Ile Cys Glu Leu Val Ser Asp Tyr Lys Glu Lys Gln Met Pro Lys Tyr Ser Ser Glu Asn Ser Asn Pro Glu Gln Asp Leu Lys Leu Thr Ser Glu Glu Glu Ser Gln Arg Leu Glu Gly Ser Glu Asn Gly Gln Pro Glu Leu Glu Asn Phe Met Ala Ile Glu Glu Met Lys Lys His Gly Ser Thr His Val Gly Phe Pro Glu Asn Leu Thr Asn Gly Ala Thr Ala Gly Asn Gly Asp Gly Leu Ile Pro Pro Arg Lys Ser Arg Thr Pro Glu Ser Gln Gln Phe Pro Asp Thr Glu Asn Glu Glu Tyr His Ser Asp Glu Gln Asn Asp Thr Gln Lys Gln Phe Cys Glu Glu Gln Asn Thr Gly Ile Leu His Asp Glu Ile Leu Ile His Glu Glu Lys Gln Ile Glu Val Val Glu Lys Met Asn Ser Glu Leu Ser Leu Ser Cys Lys Lys Glu Lys Asp Ile Leu His Glu Asn Ser Thr Leu Arg Glu Glu Ile Ala Met Leu Arg Leu Glu Leu Asp Thr Met Lys His Gln Ser Gln Leu 

<210> 380

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Lys Lys Asp Arg Ala Trp Leu Arg Cys Pro Glu Ala Val Ala Gly Phe
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teatacteaa ttgatggtta ttagacaatt ceatttettt etggttatta taaacagaaa 420
atctttcctc ttctcattac cagtaaaggc tcttggtatc tttctgttgg aatgatttct 480
atgaacttgt cttattttaa tggtgggttt tttttctggt
                                                                   520
<210> 389
<211> 365
<212> DNA
<213> Homo sapiens
<400> 389
cgttgcccca gtttgacaga aggaaaggcg gagcttattc aaagtctaga gggagtggag 60
gagttaagge tggattteag atetgeetgg ttecageege agtgtgeeet etgeteece 120
aacgactite caaataatet caccagegee ttecagetea ggegteetag aagegtettg 180
aagectatgg ccagetgtet ttgtgtteee teteaceege etgteeteae agetgagaet 240
cccaggaaac cttcagacta ccttcctctg ccttcagcaa ggggcgttgc ccacattctc 300
tgagggtcag tggaagaacc tagactccca ttgctagagg tagaaagggg aagggtgctg 360
gggag
<210> 390
<211> 221
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (221)
<223> n = A, T, C or G
<400> 390
tgeeteteea teetggeeee gaettetetg teaggaaagt ggggatggae eecatetgea 60
tacacggntt ctcatgggtg tggaacatct ctgcttgcgg tttcaggaag gcctctggct 120
getetangag tetganenga ntegttgeee cantntgaca naaggaaagg eggagettat 180
tcaaagtcta gagggagtgg aggagttaag gctggatttc a
<210> 391
<211> 325
<212> DNA
<213> Homo sapiens
```

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<220>
<221> misc_feature
<222> (1)...(325)
<223> n = A,T,C or G
<400> 391
tggagcaggt cccgaggcct ccctagagcc tggggccgac tctgtgncga tgcangcttt 60
ctctcgcgcc cagcctggag ctgctcctgg catctaccaa caatcagncg aggcgagcag 120
tagccagggc actgctgcca acagccagtc cnnataccat catgtnaccc ggtgngctct 180
naanttngat ntccanagce ctacccaten tagttetget eteccacegg ntaccagcee 240
cactgoccaq quatectaca qecagtacce tgtecegacg tetetaceta ecagtacgat 300
gagacetecg getactacta tgace
                                                                 325
<210> 392 -
<211> 277
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(277)
<223> n = A, T, C or G
<400> 392
atattgttta actccttcct ttatatcttt taacattttc atggngaaag gttcacatct 60
agteteactt nggenagngn etectaettg agtetettee eeggeetgnn eeagtngnaa 120
antaccanga accgncatgn cttaanaacn neetggtttn tgggttnntc aatgactgca 180
tgcagtgcac caccetgtee actacgtgat getgtaggat taaagtetea cagtgggegg 240
ctgaggatac agcgccgcgt cctgtgttgc tggggaa
<210> 393
<211> 566
<212> DNA
<213> Homo sapiens
<400> 393
actagtecag tgtggtggaa ttegeggeeg egtegaegga eaggteaget gtetggetea 60
gtgatetaca ttetgaagtt gtetgaaaat gtetteatga ttaaatteag eetaaaegtt 120
ttgccgggaa cactgcagag acaatgctgt gagtttccaa ccttagccca tctgcgggca 180
qaqaaqqtct agtttgtcca tcaqcattat catgatatca ggactggtta cttggttaag 240
gaggggteta ggagatetgt ecettttaga gacacettae ttataatgaa gtatttggga 300
qqqtqqtttt caaaagtaga aatgtcctgt attccgatga tcatcctgta aacattttat 360
cattetetge etgagtttta atttttgtee aaagttattt taatetatae aattaaaage 540
ttttgcctat caaaaaaaa aaaaaa
<210> 394
<211> 384
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(384)
<223> n = A, T, C or G
<400> 394
quacatacat qteecqqcac etqaqetqca qtetqacate ateqecatca eqqqeeteqe 60
tgcaaattng gaccgggcca aggctggact gctggagcgt gtgaaggagc tacaggccna 120
qcaggaggac cgggctttaa ggagttttaa gctgagtgtc actgtagacc ccaaatacca 180
teccaagatt ategggagaa agggggeagt aattacecaa ateeggttgg ageatgaegt 240
```

gaacatccag tttcctgata aggacgatgg gaaccagccc caggaccaaa ttaccatcac 300

```
agggtacgaa aagaacacag aagctgccag ggatgctata ctgagaattg tgggtqaact 360
tgagcagatg gtttctgagg acgt
<210> 395
<211> 399
<212> DNA
<213> Homo sapiens
<400> 395
ggcaaaactg tgtgacctca ataagacctc gcagatccaa ggtcaagtat cagaagtgac 60
totgacettg gactecaaga cetacateaa cageetgget atattagatg atgagecagt 120
tatcagaggt ttcatcattg cggaaattgt ggagtctaag gaaatcatgg cctctgaagt 180 attcacgtct ttccagtacc ctgagttctc tatagagttg cctaacacag gcagaattgg 240
ccagetactt gtetgeaatt gtatetteaa gaataceetg geeateeett tgaetgaegt 300
caagttctct ttggaaagcc tgggcatctc ctcactacag acctctgacc atgggacggt 360
gcagcctggt gagaccatcc aatcccaaat aaaatgcac
<210> 396
<211> 403
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(403)
<223> n = A, T, C or G
<400> 396
tggagttntc agtgcaaaca agccataaag cttcagtagc aaattactgt ctcacagaaa 60
gacattttca acttctgctc cagctgctga taaaacaaat catgtgttta gcttgactcc 120
agacaaggac aacctgttcc ttcataactc tctagagaaa aaaaggagtt gttagtagat 180
actaaaaaaa gtggatgaat aatctggata tttttcctaa aaagattcct tgaaacacat 240
taggaaaatg gagggcctta tgatcagaat gctagaatta gtccattgtg ctgaaqcaqq 300
gtttagggga gggagtgagg gataaaagaa ggaaaaaaag aagagtgaga aaacctattt 360
atcaaagcag gtgctatcac tcaatgttag gccctgctct ttt
                                                                       403
<210> 397
<211> 100
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(100)
<223> n = A, T, C or G
actagincag igiggiggaa ticgcggccg cgicgaccia naanccaici ciatagcaaa 60
tccatccccg ctcctggttg gtnacagaat gactgacaaa
                                                                       100
<210> 398
<211> 278
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(278)
<223> n = A, T, C or G
<400> 398
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```
geggeeget egacageagt teegeeageg etegeeeetg ggtggggatg tgetgeacge 60
ccacctggac atctggaagt cagcggcctg gatgaaagag cggacttcac ctggggcgat 120
teactactgt gcctcgacca gtgaggagag ctggaccgac agcgaggtgg actcatcatg 180
cteegggeag cecatecace tgtggeagtt ceteaaggag ttgctactca agececacag 240
ctatggccgc ttcattangt ggctcaacaa ggagaagg
<210> 399
<211> 298
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(298)
<223> n = A,T,C or G
<400> 399
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ggggtgccng catggagcgc atgggcgcgg gcctgggcca cggcatggat cgcgtgggct 120
ccgagatcga gcgcatgggc ctggtcatgg accgcatggg ctccgtggag cgcatgggct 180
ccqqcattqa qcqcatqqqc ccqctqqqcc tcqaccacat qqcctccanc attgancqca 240
tgggccagac catggagcgc attggctctg gcgtggagcn catgggtgcc ggcatggg
<210> 400
<211> 548
<212> DNA
<213> Homo sapiens
<400> 400
acatcaacta cttcctcatt ttaaggtatg gcagttccct tcatcccctt ttcctgcctt 60
qtacatqtac atqtatqaaa tttccttctc ttaccqaact ctctccacac atcacaaggt 120
tgagtetett ttttecaegt ttaaggggee atggeaggae ttagagttge gagttaagae 240
tgcagagggc tagagaatta tttcatacag gctttgaggc cacccatgtc acttatcccg 300 tataccctct caccatcccc ttgtctactc tgatgccccc aagatgcaac tgggcagcta 360
gttggcccca taattctggg cctttgttgt ttgttttaat tacttgggca tcccaggaag 420
ctttccagtg atctcctacc atgggccccc ctcctgggat caagcccctc ccaggccctg 480
tecceageee etectgeece ageceaeeeg ettgeettgg tgeteageee teccattggg 540
agcaggtt
<210> 401
<211> 355
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(355)
<223> n = A, T, C or G
<400> 401
actigtticca tigttatigtti ctacacatti ctacctcagt gctcctggaa acttagcttt 60
tgatgtctcc aagtagtcca ccttcattta actctttgaa actgtatcat ctttgccaag 120
taagagtggt ggcctatttc agctgctttg acaaaatgac tggctcctga cttaacgttc 180
tataaatgaa tgtgctgaag caaagtgccc atggtggcgg cgaagaagan aaagatgtgt 240
tttgttttgg actctctgtg gtcccttcca atgctgnggg tttccaacca ggggaagggt 300
cccttttgca ttgccaagtg ccataaccat gagcactact ctaccatggn tctgc
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<210> 402
<211> 407
<212> DNA
<213> Homo sapiens
```

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<220>
<221> misc feature
<222> (1) ... (407)
\langle 223 \rangle n = A, T, C or G
<400> 402
atggggcaag ctggataaag aaccaagacc cactggagta tqctqtcttc aaqaaaccca 60
totoacatgo ggtggcatao ataggotoaa aataaaggaa tggagaaaaa tatttoaago 120
aaatggaaaa cagaaaaaag caggtgttgc actcctactt tctgacaaaa cagactatgc 180
gaataaagat aaaaaagaga aggacattac aaaggtggtc ctgacctttg ataaatctca 240
ttgcttgata ccaacctggg ctgttttaat tgcccaaacc aaaaggataa tttgctgagg 300
ttgtggagct tctcccctgc agagagtccc tgatctccca aaatttggtt gagatgtaag 360
gntgattttg ctgacaactc cttttctgaa gttttactca tttccaa
                                                                    407
<210> 403
<211> 303
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (303)
<223> n = A,T,C or G
<400> 403
cagtatttat agccnaactg aaaagctagt agcaggcaag totcaaatcc aggcaccaaa 60
tectaageaa gageeatgge atggtgaaaa tgeaaaagga gagtetggee aatetacaaa 120
tagagaacaa gacctactca gtcatgaaca aaaaggcaga caccaacatg gatctcatgg 180
gggattggat attgtaatta tagagcagga agatgacagt gatcgtcatt tggcacaaca 240
tettaacaae gacegaaace cattatttae ataaaeetee atteggtaae catgttgaaa 300
gga
                                                                    303
<210> 404
<211> 225
<212> DNA
<213> Homo sapiens
<400> 404
aagtgtaact tttaaaaaatt tagtggattt tgaaaattct tagaggaaag taaaggaaaa 60
attgttaatg cactcattta cetttacatg gtgaaagtte tetettgate etacaaacag 120
acattttcca ctcgtgtttc catagttgtt aagtgtatca gatgtgttgg gcatgtgaat 180
ctccaagtgc ctgtgtaata aataaagtat ctttatttca ttcat
                                                                    225
<210> 405
<211> 334
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(334)
<223> n = A, T, C or G
<400> 405
gagetgttat actgtgagtt ctactaggaa atcatcaaat ctgagggttg tctggaggac 60
ttcaatacac ctccccccat agtgaatcag cttccagggg qtccaqtccc tctccttact 120
tcatccccat cccatgccaa aggaagaccc tccctccttg gctcacagcc ttctctaggc 180
ttcccagtgc ctccaggaca gagtgggtta tgttttcagc tccatccttg ctgtgagtgt 240
ctggtgcggt tgtgcctcca gcttctgctc agtgcttcat ggacagtgtc cagcccatgt 300
cactetecae teteteanng tggateceae ceet
```

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<210> 406
<211> 216
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (216)
<223> n = A, T, C or G
<400> 406
tttcatacct aatgagggag ttganatnac atnnaaccag gaaatgcatg gatctcaang 60
gaaacaaaca cccaataaac teggagtgge agactgacaa etgtgagaca tgcaettget 120
acnaaacaca aattinatgi tgcacccttg titctacacc tgtgggttat gacaaagaca 180
actgccaaag aatnttcaag aaggaggact gccant
                                                                    216
<210> 407
<211> 413
<212> DNA
<213> Homo sapiens
<400> 407
getgaettge tagtateate tgeatteatt gaageacaag aactteatge ettgaeteat 60
gtaaatgcaa taggattaaa aaataaattt gatatcacat ggaaacagac aaaaaatatt 120
gtacaacatt gcacccagtg tcagattcta cacctggcca ctcaggaagc aagagttaat 180
cccagaggtc tatgtcctaa tgtgttatgg caaatggatg tcatgcacgt accttcattt 240
ggaaaattgt catttgtcca tgtgacagtt gatacttatt cacatttcat atgggcaacc 300
tgccagacag gagaaagtot toccatgtta aaagacattt attatottgt tttootgtca 360
tgggagttcc agaaaaagtt aaaacagaca atgggccagg ttctgtagta aag
                                                                    413
<210> 408
<211> 183
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(183)
<223> n = A, T, C or G
<400> 408
ggagetngcc ctcaattcct ccatntctat gttancatat ttaatgtctt ttgnnattaa 60
tnettaacta qttaateett aaaqggetan ntaateetta actagteeet ecattgtgag 120
cattatectt ccagtatten cettetnttt tatttactee tteetggeta eccatgtact 180
ntt
                                                                   183
<210> 409
<211> 250
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(250)
<223> n = A, T, C or G
<400> 409
cccacgcatg ataagctett tatttetgta agteetgeta ggaaatcate aaatetgaeg 60
gtggtttggg ggacctgaac aaacctcctg taattaatca gctttcagtt tctcccccta 120
gtccctcctt caacaacata ggaggatcct ccccttcttt ctgctcacgg ccttatctag 180
gcttcccagt gcccccagga cagcgtgggc tatgtttaca gcgcntcctt gctgggggg 240
ggccntatgc
                                                                   250
```

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<210> 410
<211> 306
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (306)
<223> n = A, T, C or G
<400> 410
ggctggtttg caagaatgaa atgaatgatt ctacagctag gacttaacct tgaaatggaa 60
agtettgeaa teceatttge aggateegte tgtgeacatg cetetgtaga gageageatt 120
cccagggacc ttggaaacag ttggcactgt aaggtgcttg ctccccaaga cacatcctaa 180
aaggtgttgt aatggtgaaa accgcttcct tctttattgc cccttcttat ttatgtgaac 240
nactggttgg ctttttttgn atctttttta aactggaaag ttcaattgng aaaatgaata 300
tcntgc
<210> 411
<211> 261
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(261)
<223> n = A, T, C or G
<400> 411
agagatattn cttaggtnaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatettttg tatttaagga ttetgagatt ttgettgage aggattagat aaggetgtte 120
tttaaatgto tgaaatggaa cagatttoaa aaaaaaacco cacaatotag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttacccat cagttccagc 240
cttctctcaa ggngaggcaa a
                                                                   261
<210> 412
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
<400> 412
gttcaatgtt acctgacatt tctacaacac cccactcacc gatgtattcg ttgcccagtg 60
qqaacatacc agcctgaatt tggaaaaaat aattgtgttt cttgcccagg aaatactacg 120
actgactttg atggctccac aaacataacc cagtgtaaaa acagaagatg tggaggggag 180
ctgggagatt tcactgggta cattgaattc ccaaactacc cangcaatta cccagccaac 240
                                                                   241
<210> 413
<211> 231
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (231)
<223> n = A, T, C or G
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<400> 413
aactettaca atecaagtga eteatetgtg tgettgaate etttecaetg teteatetee 60
ctcatccaag tttctagtac cttctctttg ttgtgaagga taatcaaact gaacaacaaa 120
aagtttactc tecteatttg gaacetaaaa actetettet teetgggtet gagggeteea 180
agaatccttg aatcanttct cagatcattg gggacaccan atcaggaacc t
<210> 414
<211> 234
<212> DNA
<213> Homo sapiens
<400> 414
actgtccatg aagcactgag cagaagctgg aggcacaacg caccagacac tcacagcaag 60
gatggagctg aaaacataac ccactctgtc ctggaggcac tgggaagcct agagaaggct 120
gtgagccaag gagggagggt cttcctttgg catgggatgg ggatgaagta aggagaggga 180
ctggaccccc tggaagctga ttcactatgg ggggaggtgt attgaagtcc tcca
<210> 415
<211> 217
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(217)
<223> n = A,T,C or G
<400> 415
gcataggatt aagactgagt atcttttcta cattctttta actttctaag gggcacttct 60
caaaacacaq accaqqtaqc aaatctccac tqctctaaqq ntctcaccac cactttctca 120
cacctagcaa tagtagaatt cagtcctact tctgaggcca gaagaatggt tcagaaaaat 180
antggattat aaaaaataac aattaagaaa aataatc
<210> 416
<211> 213
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(213)
<223> n = A, T, C or G
<400> 416
atgcatatnt aaagganact gcctcgcttt tagaagacat ctggnctgct ctctgcatga 60
ggcacagcag taaagctett tgatteecag aateaagaac teteceette agactattae 120
cgaatgcaag gtggttaatt gaaggccact aattgatgct caaatagaag gatattgact 180
atattggaac agatggagtc tctactacaa aag
<210> 417
<211> 303
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(303)
<223> n = A, T, C or G
<400> 417
nagtottcag gcccatcagg gaagttcaca ctggagagaa gtcatacata tgtactgtat 60
```

```
gtgggaaagg ctttactctg agttcaaatc ttcaagccca tcagagagtc cacactggag 120
agaaqccata caaatqcaat qagtqtqqqa agaqcttcag qaqqqattcc cattatcaaq 180
ttcatctagt ggtccacaca ggagagaaac cctataaatg tgagatatgt gggaagggct 240
tcantcaaag ttcgtatctt caaatccatc ngaaggncca cagtatanan aaacctttta 300
agt
<210> 418
<211> 328
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(328)
<223> n = A, T, C or G
<400> 418
tttttggcgg tggtggggca gggacgggac angagtctca ctctgttgcc caggctggag 60
tgcacaggca tgatctcggc tcactacaac ccctgcctcc catgtccaag cgattcttgt 120
gcctcagcct tccctgtagc tagaattaca ggcacatgcc accacaccca gctagttttt 180
gtatttttag tagagacagg gtttcaccat gttggccagg ctggtctcaa actcctnacc 240
tcagngqtca ggctggtctc aaactcctga cctcaaqtga tctgcccacc tcagcctccc 300
aaagtgctan gattacaggc cgtgagcc
                                                                   328
<210> 419
<211> 389
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(389)
<223> n = A, T, C or G
<400> 419
ceteeteaag aeggeetgtg gteegeetee eggeaaceaa gaageetgea gtgeeatatg 60
accectgage catggactgg agectgaaag geagegtaea eeetgeteet gatettgetg 120
cttgtttcct ctctgtggct ccattcatag cacagitgtt gcactgaggc ttgtgcaggc 180
cgagcaaggc caagctggct caaagagcaa ccagtcaact ctgccacggt qtgccaggca 240
coggttetec agecaccaac etcacteget eccgeaaatg geacateagt tettetacee 300
taaaggtagg accaaagggc atctgctttt ctgaagtcct ctgctctatc agccatcacg 360
tggcagccac tcnggctgtg tcgacgcgg
                                                                   389
<210> 420
<211> 408
<212> DNA
<213> Homo sapiens
<400> 420
gttcctccta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcctt agccttggct tcttgtttct gctttttttc tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
qccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatataqaaa attottgaat gagtootata aacatgaaca ggtttatatt cqaaqcacag 360
acgttgaccg gactttgatg aagtgctatg acaaacctgg caagcccg
                                                                   408
<210> 421
<211> 352
<212> DNA
<213> Homo sapiens
```

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<220>
<221> misc_feature
<222> (1) ... (352)
<223> n = A, T, C or G
<400> 421
qctcaaaaat ctttttactg atnggcatgg ctacacaatc attgactatt acggaggcca 60
gaggagaatg aggcctggcc tgggagccct gtgcctacta naagcacatt agattatcca 120
ttcactgaca gaacaggtct tttttgggtc cttcttctcc accacnatat acttgcagtc 180
ctccttcttg aagattcttt ggcagttgtc tttgtcataa cccacaggtg tagaaacaag 240
ggtgcaacat gaaatttctg tttcgtagca agtgcatgtc tcacaagttg gcangtctgc 300
cacteegagt ttattgggtg tttgttteet ttgagateea tgeattteet qq
<210> 422
<211> 337
<212> DNA
<213> Homo sapiens
atgccaccat gctggcaatg cagcgggcgg tcgaaggcct gcatatccag cccaagctqq 60
cgatgatcga cggcaaccgt tgcccgaagt tgccgatgcc agccgaagcg gtggtcaagg 120
gegatageaa ggtgeeggeg ategeggegg egteaateet ggeeaaggte ageegtgate 180
gtgaaatggc agctgtcgaa ttgatctacc cgggttatgg catcggcqqq cataaqqqct 240
atccgacacc ggtgcacctg gaagccttgc agcggctggg gccgacgccg attcaccgac 300
gettetteeg eeggtaegge tggeetatga aaattat
                                                                    337
<210> 423
<211> 310
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(310)
<223> n = A, T, C or G
<400> 423
gctcaaaaat ctttttactg atatggcatg gctacacaat cattgactat tagaggccag 60
aggagaatga ggcctggcct gggagccctg tgcctactan aagcncatta gattatccat 120
teactgacag aacaggictt tittgggtee tietteteea ceacgatata ettgeagtee 180
teettettga agattetttg geagttgtet ttgteataac ceacaggtgt anaaacaagg 240
gtgcaacatg aaatttctgt ttcgtagcaa gtgcatgtct cacagttgtc aagtctgccc 300
tccgagttta
                                                                   310
<210> 424
<211> 370
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(370)
<223> n = A, T, C or G
gctcaaaaat ctttttactg ataggcatgg ctacacaatc attgactatt agaggccaga 60
ggagaatgag gcctggcctg ggagccctgt gcctactaga agcacattag attaccatt 120
cactgacaga acaggtettt tttgggteet tetteteeac cacgatatac ttgcagteet 180
ccttcttgaa gattctttgg cagttgtctt tgtcataacc cacagqtgta qaaacatcct 240
ggttgaatet cetggaacte ceteattagg tatgaaatag catgatgcat tgcataaagt 300
cacgaaggtg gcaaagatca caacgctgcc cagganaaca ttcattgtga taagcaggac 360
tccgtcgacg
```

```
<210> 425
<211> 216
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(216)
<223> n = A, T, C or G
<400> 425
taacaacnca acatcaaggn aaananaaca ggaatggntg actntgcata aatnggccga 120
anattateca ttainttaag ggttgactte aggntacage acacagacaa acatgeecag 180
gaggntntca ggaccgctcg atgtnttntg aggagg
<210> 426
<211> 596
<212> DNA
<213> Homo sapiens
<400> 426
cttccagtga ggataaccct gttgccccgg gccgaggttc tccattaggc tctgattgat 60
tggcagtcag tgatggaagg gtgttctgat cattccgact gccccaaggg tcgctggcca 120
getetetgtt ttgetgagtt ggeagtagga eetaatttgt taattaagag tagatggtga 180
gctgtccttg tattttgatt aacctaatgg ccttcccagc acgactcgga ttcagctgga 240
gacatcacgg caactttaa tgaaatgatt tgaagggcca ttaagaggca cttcccgtta 300
ttaggcagtt catctgcact gataacttct tggcagctga gctgqtcgga gctgtggccc 360
aaacgcacac ttggcttttg gttttgagat acaactctta atcttttagt catgcttgag 420
ggtggatggc cttttcagct ttaacccaat ttgcactgcc ttggaagtgt agccaggaga 480
atacactcat atactcgtgg gcttagaggc cacagcagat gtcattggtc tactgcctga 540
gtcccgctgg tcccatccca ggaccttcca tcggcgagta cctgggagcc cgtgct
<210> 427
<211> 107
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(107)
<223> n = A,T,C or G
<400> 427
gaagaattca agttaggttt attcaaaggg cttacngaga atcctanacc caggncccag 60
cccgggagca gccttanaga gctcctgttt gactgcccgg ctcagng
                                                                107
<210> 428
<211> 38
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(38)
<223> n = A, T, C or G
<400> 428
gaacttccna anaangactt tattcactat tttacatt
                                                                38
<210> 429
```

```
<211> 544
<212> DNA
<213> Homo sapiens
<400> 429
ctttgctgga cggaataaaa gtggacgcaa gcatgacctc ctgatgaggg cgctgcattt 60
attgaagage ggetgeagee etgeggttea gattaaaate egagaattgt atagaegeeg 120
atatccacga actettgaag gactttctga tttatccaca atcaaatcat cggttttcag 180
tttggatggt ggctcatcac ctgtagaacc tgacttggcc gtggctggaa tccactcqtt 240
geettecact teagttacae etcacteace atcetetect gttggttetg tgetgettea 300
agatactaag cccacatttg agatgcagca gccatctccc ccaattcctc ctgtccatcc 360
tgatgtgcag ttaaaaaatc tgccctttta tgatgtcctt gatgttctca tcaagcccac 420
gagtitagti caaagcagta ticagcgatt tcaagagaag titittatti tigciitigac 480
acctcaacaa gttagagaga tatgcatatc cagggatttt ttgccaggtg gtaggagaga 540
ttat
<210> 430
<211> 507
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (507)
<223> n = A, T, C or G
<400> 430
cttatcncaa tggggctccc aaacttggct gtgcagtgga aactccgggg gaattttgaa 60
gaacactgac acccatette cacceegaca etetgattta attgggetge agtgagaaca 120
gagcatcaat ttaaaaaagct gcccagaatg ttntcctggg cagcgttgtg atctttgccn 180
cettegtgae tttatgeaat geateatget attteatace taatgaggga gtteeaggag 240
attcaaccag gatgtttcta enectgtggg ttatgacaaa gacaactgee aaagaatntt 300
caagaaggag gactgcaagt atatcgtggt ggagaagaag gacccaaaaa agacctgttc 360
tgtcagtgaa tggataatot aatgtgotto tagtaggoac agggotocca ggocaggoot 420
catteteete tggeetetaa tagteaatga ttgtgtagee atgeetatea gtaaaaagat 480
ttttgagcaa aaaaaaaaa aaaaaaa
                                                                   507
<210> 431
<211> 392
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(392)
<223> n = A, T, C or G
<400> 431
gaaaattcag aatggataaa aacaaatgaa gtacaaaata tttcagattt acatagcgat 60
aaacaagaaa gcacttatca ggaggactta caaatggaag tacactctan aaccatcatc 120
tatcatggct aaatgtgaga ttagcacagc tgtattattt gtacattgca aacacctaga 180
aagagatigg aaacaaaatc ccaggagttt tittgtgtgtgga gtcctgggtt ttccaacaga 240
catcattcca gcattctgag attagggnga ttggggatca ttctggagtt ggaatgttca 300
acaaaagtga tgttgttagg taaaatgtac aacttctgga tctatgcaga cattgaaggt 360
gcaatgagtc tggcttttac tctgctgttt ct
                                                                   392
<210> 432
<211> 387
<212> DNA
<213> Homo sapiens
<220>
```

```
<221> misc feature
<222> (1)...(387)
<223> n = A, T, C or G
<400> 432
ggtatccnta cataatcaaa tatagctgta gtacatgttt tcattggngt agattaccac 60
anatycang cancatytyt agatetetty tettattett ttytetatan tactytatty 120
ngtagtccaa gctctcggna gtccagccac tgngaaacat gctcccttta gattaacctc 180
gtggacnetn ttgttgnatt gtetgaactg tagngcoctg tattttgctt etgtetgnga 240
attotqttqc ttotqqqqca tttccttgng atgcagagga ccaccacaca gatgacagca 300
atctgaattg ntccaatcac agctgcgatt aagacatact gaaatcgtac aggaccggga 360
                                                                     387
acaacqtata qaacactgga gtccttt
<210> 433
<211> 281
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (281)
<223> n = A, T, C or G
<400> 433
ttcaactage anagaanact getteagggn gtgtaaaatg aaaggettee aegeagttat 60
ctgattaaag aacactaaga gagggacaag gctagaagcc gcaggatgtc tacactatag 120
caggenetat ttgggttgge tggaggaget gtggaaaaca tggagagatt ggegetggag 180
ategeegtgg ctattecten ttgntattae accagngagg ntetetgtnt geceaetggt 240
                                                                     281
tnnaaaaccg ntatacaata atgatagaat aggacacaca t
<210> 434
<211> 484
<212> DNA
<213> Homo sapiens
<400> 434
ttttaaaata agcatttagt gctcagtccc tactgagtac tctttctctc ccctcctctg 60
aatttaattc titcaacttg caattigcaa ggattacaca titcactgtg atgtatattg 120
tqttqcaaaa aaaaaaaaqt qtctttgttt aaaattactt ggtttgtgaa tccatcttgc 180
tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa acatctgaag 240
agctagteta teageatetg acaggtgaat tggatggtte teagaaceat tteacceaga 300
cagcctqttt ctatcctgtt taataaatta gtttgggttc tctacatgca taacaaaccc 360
toctccaatc totcacataa aagtctotoa cttoaagttt agtcaocacc cccaccaaac 420
tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataaag tacccatgtc 480
                                                                     484
ttta
<210> 435
<211> 424
<212> DNA
<213> Homo sapiens
<400> 435
gegeegetea gageaggtea etttetgeet tecaegteet eetteaagga ageeceatgt 60
qqqtaqcttt caatatcgca ggttcttact cctctgcctc tataagctca aacccaccaa 120
cqatcqqqca agtaaacccc ctccctcgcc gacttcggaa ctggcgagag ttcagcgcag 180
atgggcctgt ggggaggggg caagatagat gagggggagc ggcatggtgc ggggtgaccc 240
cttggagaga ggaaaaaggc cacaagaggg gctgccaccg ccactaacgg agatggccct 300 ggtagagacc tttgggggtc tggaacctct ggactcccca tgctctaact cccacactct 360
qctatcaqaa acttaaactt gaggattttc tctgtttttc actcgcaata aattcagagc 420
aaac
```

```
<211> 667
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(667)
<223> n = A,T,C or G
<400> 436
accttgggaa nacteteaca atataaaggg tegtagaett tacteeaaat teeaaaaagg 60
teetggeeat gtaateetga aagtttteee aaggtageta taaaateett ataagggtge 120
agoctottot ggaattooto tgatttoaaa gtotoactot caagttottg aaaacgaggg 180
cagtteetga aaggeaggta tageaactga tetteagaaa gaggaactgt gtgcaceggg 240 atgggetgee agagtaggat aggatteeag atgetgacae ettetggggg aaacaggget 300
gecaggitty teatageact cateaaagte eggicaacgi etgigetteg aatataaace 360
tgttcatgtt tataggactc attcaagaat tttctatatc tctttcttat atactctcca 420
agttcataat gctgctccat gcccagctgg gtgagttggc caaatccttg tggccatgag 480
gatteettta tggggteagt gggaaaggtg teaatgggae tteggtetee atgeegaaae 540
accaaagtca caaacttcaa ctccttggct agtacacttc ggtctagcca gaaaaaaagc 600
agaaacaaga agccaagget aaggettget geeetgeeag gaggaggggt geagetetea 660
tgttgag
<210> 437
<211> 693
<212> DNA
<213> Homo sapiens
<400> 437
ctacgtetea acceteattt ttaggtaagg aatettaagt ccaaagatat taagtgacte 60
acacaqccaq qtaaqqaaaq ctqqattqqc acactaqqac tctaccatac cqqqttttqt 120
taaageteag gttaggagge tgataagett ggaaggaact teagacaget tttteagate 180
ataaaagata attettagee catgttette teeagageag acetgaaatg acageacage 240
aggtactect ctattttcac ccctcttgct tctactctct ggcagtcaga cctgtgggag 300
gccatgggag aaagcagctc tctggatgtt tgtacagatc atggactatt ctctgtggac 360
cattleteca ggttacceta ggtgteacta ttggggggac agecageate tttagettte 420
atttgagttt ctgtctgtct tcagtagagg aaacttttgc tcttcacact tcacatctga 480
acacctaact gctgttgctc ctgaggtggt gaaagacaga tatagagctt acagtattta 540
tectatttet aggeactgag ggetgtgggg tacettgtgg tgeeaaaaca gateetgttt 600
taaggacatg ttgcttcaga gatgtctgta actatctggg ggctctgttg gctctttacc 660
ctgcatcatg tgctctcttg gctgaaaatg acc
<210> 438
<211> 360
<212> DNA
<213> Homo sapiens
<400> 438
ctgcttatca caatgaatgt tctcctgggc agcgttgtga tctttgccac cttcgtgact 60
ttatgcaatg catcatgcta tttcatacct aatgagggag ttccaggaga ttcaaccagg 120
atgtttctac acctgtgggt tatgacaaag acaactgcca aagaatcttc aagaaggagg 180
actgcaagta tatctggtgg agaagaagga cccaaaaaag acctgttctg tcagtgaatg 240
gataatetaa tgtgetteta gtaggeacag ggeteecagg ceaggeetea tteteetetg 300
qcctctaata qtcaataatt gtgtagccat gcctatcagt aaaaaqattt ttgagcaaac 360
<210> 439
<211> 431
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
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<222> (1)...(431)
<223> n = A, T, C \text{ or } G
<400> 439
qttcctnnta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcctt agccttggct tcttgtttct gctttttttc tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
qccaactcac ccagctgggc atggagcagc attatgaact tqqagagtat ataagaaaga 300
gatatagaaa attottgaat gagtootata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
aatttagtag t
<210> 440
<211> 523
<212> DNA
<213> Homo sapiens
<400> 440
agagataaag cttaggtcaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatettttg tatttaagga ttetgagatt ttgettgage aggattagat aaggetgtte 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaaacca atttacccat caqttccaqc 240
cttctctcaa ggagaggcaa agaaaggaga tacagtggag acatctggaa agttttctcc 300
actggaaaac tgctactatc tgtttttata tttctgttaa aatatatgag gctacagaac 360
taaaaattaa aacctetttg tgteeettgg teetggaaca tttatgttee ttttaaagaa 420
acaaaaatca aactttacag aaagatttga tgtatgtaat acatatagca gctcttgaag 480
tatatatatc atagcaaata agtcatctga tgagaacaag cta
                                                                   523
<210> 441
<211> 430
<212> DNA
<213> Homo sapiens
gttectecta actectgeca gaaacagete tecteaacat gagagetgea eccetectee 60
tggccagggc agcaagcett agcettgget tettgtttet gettittte tggctagace 120
gaagtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attettgaat gagteetata aacatgaaca ggtttatatt egaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
aatttagtag
                                                                   430
<210> 442
<211> 362
<212> DNA
<213> Homo sapiens
<400> 442
ctaaggaatt agtagtgttc ccatcacttg tttggagtgt gctattctaa aagattttga 60
tttcctqqaa tgacaattat attttaactt tggtggggga aagagttata ggaccacagt 120
cttcacttct gatacttgta aattaatctt ttattgcact tgttttgacc attaagctat 180
atgtttagaa atggtcattt tacggaaaaa ttagaaaaat tctgataata gtgcagaata 240
aatgaattaa tgttttactt aatttatatt gaactgtcaa tgacaaataa aaattctttt 300
tgattatttt ttgttttcat ttaccagaat aaaaactaag aattaaaagt ttgattacag 360
                                                                   362
<210> 443
<211> 624
<212> DNA
<213> Homo sapiens
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<220>
<221> misc feature
<222> (1)...(624)
<223> n = A, T, C or G
<400> 443
tttttttttt gcaacacaat atacatcaca qtgaaatgtg taatccttgc aaattgcaag 60
ttgaaagaat taaattcaga ggaggggaga gaaagagtac tcagtaggga ctgagcactä 120
aatgettatt ttaaaagaaa tgtaaagage agaaageaat teaggetaee etgeetttig 180
tgctggctag tactccggtc ggtgtcagca gcacgtggca ttgaacattg caatgtggag 240
cccaaaccac agaaaatggg gtgaaattgg ccaactttct attaacttgg cttcctgttt 300
tataaaatat tgtgaataat atcacctact tcaaagggca gttatgaggc ttaaatgaac 360
taacgcctac aaaacactta aacatagata acataggtgc aagtactatg tatctggtac 420
atggtaaaca teettattat taaagteaac getaaaatga atgtgtgtgc atatgetaat 480
agtacagaga gagggcactt aaaccaacta agggcctgga gggaaggttt cctggaaaga 540
ngatgcttgt gctgggtcca aatcttggtc tactatgacc ttggccaaat tatttaaact 600
ttgtccctat ctgctaaaca gatc
<210> 444
<211> 425
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(425)
<223> n = A, T, C or G
<400> 444
gcacatcatt nntcttgcat tctttgagaa taagaagatc agtaaatagt tcagaagtgg 60
gaagetttgt ccaggeetgt gtgtgaacce aatgttttge ttagaaatag aacaagtaag 120
ttcattgcta tagcataaca caaaatttgc ataagtggtg gtcagcaaat ccttgaatgc 180
tgcttaatgt gagaggttgg taaaatcctt tgtgcaacac tctaactccc tgaatgtttt 240
gctgtgctgg gacctgtgca tgccagacaa ggccaagctg gctgaaagag caaccagcca 300 cctctgcaat ctgccacctc ctgctggcag gatttgttt tgcatcctgt gaagagccaa 360
ggaggcacca gggcataagt gagtagactt atggtcgacg cggccgcgaa tttagtagta 420
gtaga
<210> 445
<211> 414
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(414)
<223> n = A, T, C or G
<400> 445
catgittatg ntittggatt actitgggca cetagtgttt ctaaatcgtc tatcattctt 60
ttctgttttt caaaagcaga gatggccaga gtctcaacaa actgtatctt caagtctttg 120
tgaaattett tgcatgtggc agattattgg atgtagttte etttaactag catataaate 180
tggtgtgttt cagataaatg aacagcaaaa tgtggtggaa ttaccatttg gaacattgtg 240
aatgaaaaat tgtgtctcta gattatgtaa caaataacta tttcctaacc attgatcttt 300
ggatttttat aatcctactc acaaatgact aggcttctcc tcttgtattt tgaagcagtg 360
tgggtgctgg attgataaaa aaaaaaaaag tcgacgcggc cgcgaattta gtag
<210> 446
<211> 631
<212> DNA
<213> Homo sapiens
```

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<220>
<221> misc_feature
<222> (1)...(631)
<223> n = A, T, C or G
<400> 446
acaaattaga anaaagtgcc agagaacacc acataccttg teeggaacat tacaatggct 60
tetgeatgea tgggaagtgt gageatteta teaatatgea ggageeatet tgeaggtgtg 120
atgctggtta tactggacaa cactgtgaaa aaaaggacta cagtgttcta tacgttgttc 180
ccggtcctgt acgatttcag tatgtcttaa tcgcagctgt gattggaaca attcagattg 240
etgtcatetg tgtggtggte etetgeatea caagggeeaa aetttaggta atageattgg 300
actgagattt gtaaactttc caaccttcca ggaaatgccc cagaagcaac agaattcaca 360
gacagaagca aaatacaggg cactacagtt cagacaatac aacaagagcg tccacgaggt 420
taatctaaag ggagcatgtt tcacagtggc tggactaccg agagcttgga ctacacaata 480
cagtattata gacaaaagaa taagacaaga gatctacaca tgttgccttg catttgtggt 540
aatctacacc aatgaaaaca tgtactacag ctatatttga ttatgtatgg atatatttga 600
aatagtatac attgtcttga tgttttttct g
<210> 447
<211> 585
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(585)
<223> n = A,T,C or G
<400> 447
ccttgggaaa antntcacaa tataaagggt cgtagacttt actccaaatt ccaaaaaggt 60
cctqqccatq taatcctqaa aqttttccca aqqtaqctat aaaatcctta taaqqqtqca 120
gcctcttctg gaattcctct gatttcaaag tctcactctc aagttcttga aaacgagggc 180
agtteetgaa aggeaggtat ageaactgat etteagaaag aggaactgtg tgeaceggga 240
tgggctgcca gagtaggata ggattccaga tgctgacacc ttctggggga aacagggctg 300
ccaggtttgt catagcactc atcaaagtcc ggtcaacgtc tgtgcttcga atataaacct 360
gttcatgttt ataggactca ttcaagaatt ttctatatct ctttcttata tactctccaa 420
gttcataatg ctgctccatg cccagctggg tgagttggcc aaatccttgt ggccatgagg 480
attectttat ggggteagtg ggaaaggtgt caatgggaet teggteteea tgeegaaaca 540
ccaaagtcac aaacttcaac tccttggcta gtacacttcg gtcta
                                                                   585
<210> 448
<211> 93
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (93)
<223> n = A, T, C or G
<400> 448
tgctcgtggg tcattctgan nnccgaactg accntgccag ccctgccgan gggccnccat 60
ggctccctag tgccctggag agganggggc tag
<210> 449
<211> 706
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
```

```
<222> (1)...(706)
<223> n = A, T, C or G
<400> 449
ccaaqttcat gctntgtgct qqacqctqqa cagggggcaa aagcnnttqc tcqtqqqtca 60
ttotgancac egaactgace atgecagece tgeegatggt cetecatgge tecetagtge 120
cctggagagg aggtgtctag tcagagagta gtcctggaag gtggcctctg ngaggagcca 180
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<210> 450
<211> 493
<212> DNA
<213> Homo sapiens
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<210> 452
<211> 51
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<222> (1)...(51)
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<210> 453
<211> 317
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(317)
\langle 223 \rangle n = A,T,C or G
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ttcacccana cagcctgttt ctatcctgtt taataaatta gtttgggttc tctacatgca 180
taacaaaccc tgctccaatc tgtcacataa aagtctgtga cttgaagttt antcagcacc 240
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agaagaccaa attottotgo atoccagott goaaacaaaa ttgttottot aggtotocac 180
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<212> DNA
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<211> 231
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<211> 231
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## 146

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catttgacag gtgtcttttc ctctggacct cggtgtcccc atctgagtga gaaaaggcag 180
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<211> 3112
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<212> DNA <213> Homo sapiens <400> 468

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<400> 469

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Ala	Thr 50	Asn	Ile	Thr	Pro	Lys 55	His	Asn	Met	Lys	Ala 60	Phe	Leu	Asp	Glu	
Leu 65	Lys	Ala	Glu	Asn	Ile 70	Lys	Lys	Phe	Leu	Tyr 75		Phe	Thr	Gln	Ile 80	
Pro	His	Leu	Ala	Gly 85		Glu	Gln	Asn	Phe 90	Gln	Leu	Ala	Lys	Gln 95	Ile	•
Gln	Ser	Gln	Trp 100	Lys	Glu	Phe	Gly	Leu 105	Asp	Ser	Val	Glu	Leu 110	Ala	His	
Tyr	Asp	Val 115	Leu	Leu	Ser	Tyr	Pro 120	Asn	Lys	Thr	His	Pro 125	Asn	Tyr	Tle	
Ser	Ile 130	Ile	Asn	Glu	Asp	Gly 135	Asn	Glu	Ile	Phe	Asn 140	Thr	Ser	Leu	Phe	
Glu 145	Pro	Pro	Pro	Pro	Gly 150	Tyr	Glu	Asn	Val	Ser 155	Asp	Ile	Val	Pro	Pro 160	
Phe	Ser	Ala	Phe	Ser 165	Pro	Gln	Gly	Met	Pro 170	Glu	Gly	Asp	Leu	Val 175	Tyr	•
Val	Asn	Tyr	Ala 180	Arg	Thr	Glu	Asp	Phe 185	Phe	Lys	Leu	Glu	Arg 190	Asp	Met	
Lys	lle	Asn 195	Суз	Ser	Gly	Lys	11e 200	Val	Ile	Ala	Arg	Tyr 205	Gly	Lys	Val	•
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Val 225	Ile	Leu	Tyr	Ser	Asp 230	Pro	Ala	Asp	Tyr	Phe 235	Ala	Pro	Gly	Val	Lys 240	
Ser	Tyr	Pro	Asp	Gly 245	Trp	Asn	Leu	Pro	Gly 250	Gly	Gly	Val	Gln	Arg 255	Gly,	
Asn	Ile	Leu	Asn	Leu	Asn	Gly	Ala	Gly	Asp	Pro	Leu	Thr	Pro	Gly	Tyr	*

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Phe	Ser	Thr	Gln 340	Lys	Val	Lys	Met	His 345	Ile	His	Ser	Thr	Asn 350	Glu	Val
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Asp	Arg 370	Tyr	Val	Ile	Leu	Gly 375	Gly	His	Arg	Asp	Ser 380	Trp	Val	Phe	Gly
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Glu	Trp	Ala 435	Glu	Glu	Asn	Ser	Arg 440	Leu	Leu	Gln	Glu	Arg 445	Gly	Val	Ala
Tyr	Ile 450	Asn	Ala	Asp	Ser	Ser 455	Ile	Glu	Gly	Asn	Tyr 460	Thr	Leu	Arg	Val
Asp 465	Суз	Thr	Pro	Leu	Met 470	Tyr	Ser	Leu	Val	His 475	Asn	Leu	Thr	Lys	Glu 480
Leu	Lys	Ser	Pro	Asp 485	Glu	Gly	Phe	Glu	Gly 490	Lys	Ser	Leu	Tyr	Glu 495	
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Ser	Lys	Leu 515	Gly	Ser	Gly	Asn	Asp 520	Phe	Glu	Val	Phe	Phe 525	Gln	Arg	Leu
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Lys 545	Phe	Ser	Gly	Tyr	Pro 550	Leu	Tyr	His	Ser	Val 555	Tyr	Glu	Thr	Tyr	Glu 560
Leu	Val	Glu	Lys	Phe 565	Tyr	Asp	Pro	Met	Phe 570	Lys	Туг	His	Leu	Thr 575	Val
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 Phe Sp5
 Asp Sp5
 Cys Sp5
 Arg Asp Sp5
 Arg Asp Sp5
 Tyr Ala 600
 Ala Val Val Leu Arg Sp5
 Leu Arg Sp5
 Lys Tyr Ala Sp5
 Asp Sp5
 Lys Sp5
 Ala Sp7
 Ala S

Phe Pro Gly Ile Tyr Asp Ala Leu Phe Asp Ile Glu Ser Lys Val Asp 705 710 715 720

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Pro Ile Asp Thr Phe Pro Thr Asp Pro Ile Lys Glu Ser Ser Trp Pro 50 55 60

Gln Gly Phe Gly Gln Leu Thr Gln Leu Gly Met Glu Gln His Tyr Glu 65 70 75 80

Leu Gly Glu Tyr Ile Arg Lys Arg Tyr Arg Lys Phe Leu Asn Glu Ser 85 90 95

Tyr Lys His Glu Gln Val Tyr Ile Arg Ser Thr Asp Val Asp Arg Thr 100 105 110

Leu Met Ser Ala Met Thr Asn Leu Ala Ala Leu Phe Pro Pro Glu Gly 115 120 125

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Суз	Pro	Arg	Phe	Gln 165	Glu	Leu	Glu	Ser	Glu 170	Thr	Leu	Lys	Ser	Glu 175	Glu
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Val	Tyr 210	Asp	Pro	Leu	Tyr	Cys 215	Glu	Ser	Val	His	Asn 220	Phe	Thr	Leu	Pro
Ser 225	Trp	Ala	Thr	Glu	Asp 230	Thr	Met	Thr	Lys	Leu 235	Arg	Glu	Leu	Ser	Glu 240
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Arg	Leu	Gln	Gly 260	Gly	Val	Leu	Val	Asn 265	Glu	Ile	Leu	Asn	His 270	Met	Lys
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Lys His Ser Gln Pro Trp Gln Val Leu Val Ala Ser Arg Gly Arg Ala Val Cys Gly Gly Val Leu Val His Pro Gln Trp Val Leu Thr Ala Ala His Cys Ile Arg Asn Lys Ser Val Ile Leu Leu Gly Arg His Ser Leu Phe His Pro Glu Asp Thr Gly Gln Val Phe Gln Val Ser His Ser Phe Pro His Pro Leu Tyr Asp Met Ser Leu Leu Lys Asn Arg Phe Leu Arg 100 105 Pro Gly Asp Asp Ser Ser His Asp Leu Met Leu Leu Arg Leu Ser Glu Pro Ala Glu Leu Thr Asp Ala Val Lys Val Met Asp Leu Pro Thr Gln Glu Pro Ala Leu Gly Thr Thr Cys Tyr Ala Ser Gly Trp Gly Ser Ile Glu Pro Glu Glu Phe Leu Thr Pro Lys Lys Leu Gln Cys Val Asp Leu His Val Ile Ser Asn Asp Val Cys Ala Gln Val His Pro Gln Lys Val 185 Thr Lys Phe Met Leu Cys Ala Gly Arg Trp Thr Gly Gly Lys Ser Thr Cys Ser Gly Asp Ser Gly Gly Pro Leu Val Cys Asn Gly Val Leu Gln 215 Gly Ile Thr Ser Trp Gly Ser Glu Pro Cys Ala Leu Pro Glu Arg Pro Ser Leu Tyr Thr Lys Val Val His Tyr Arg Lys Trp Ile Lys Asp Thr 250

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Met	Leu 130	Leu	Arg	Leu	Ser	Glu 135	Pro	Ala	Glu	Leu	Thr 140	Asp	Ala	Val	Lys
Val 145	Met	Asp	Leu	Pro	Thr 150	Gln	Glu	Pro	Ala	Leu 155	Gly	Thr	Thr	Cys	Tyr 160
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_			180		Asp			185					190		
Gln	Val	His 195	Pro	Gln	Lys	Val	Thr 200	Lys	Phe	Met	Leu	Cys 205	Ala	Gly	Arg
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_				245	Arg				250					255	
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		•		325	Cys				330					335	
			340		Cys			345		_			350		
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Ala	Ser 370	Leu	Ser	Val	Arg	His 375	Pro	Glu	Tyr	Asn	Arg 380	Pro	Leu	Leu	Ala

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Pro	Суз	Gly	Gln 500	Val	Gly	Val	Pro	Gly 505	Val	Tyr	Thr	Asn	Leu 510	Cys	Lys
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Gln	Arg 530	Leu	Trp	Val	Ser	Arg 535	Leu	Leu	Arg	His	Arg 540	Lys	Ala	Gln	Leu
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Cys	Val	Pro 595	Leu	Leu	Gly	Ser	Ala 600	Ser	Asp	His	Trp	Arg 605	Gly	Arg	Tyr
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Val	Tyr 690	Ala	Phe	Met	Ile	Ser 695	Leu	Gly	Gly	Cys	Leu 700	Gly	Tyr	Leu	Leu
Pro	Ala	Ile	Asp	Trp	Asp	Thr	Ser	Ala	Leu	Ala	Pro	Tvr	Leu	Glv	Thr

705					710					715					720
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Val	Ala	Ala	Thr 740	Leu	Leu	Val	Ala	Glu 745	Glu	Ala	Ala	Leu	Gly 750	Pro	Thr
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Pro	Cys 770	Arg	Ala	Arg	Leu	Ala 775	Phe	Arg	Asn	Leu	Gly 780	Ala	Leu	Leu	Pro
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Ala	Glu	Pro 835	Gly	Thr	Glu	Ala	Arg 840	Arg	His	Tyr	Asp	Glu 845	Gly	Val	Arg
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Leu	Ser	His	Ser 900	Val	Ala	Val	Val	Thr 905	Ala	Ser	Ala	Ala	Leu 910	Thr	Gly
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Tyr	His 930	Arg	Glu	Lys	Gln	Val 935	Phe	Leu	Pro	Lys	Tyr 940	Arg	Gly	Asp	Thr
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Phe 1025		Leu	Ser	Gln	Val 103		Pro	Ser	Leu		Met )35	Gly	Ser	Ile	Val 1040

Gln Leu Ser Gln Ser Val Thr Ala Tyr Met Val Ser Ala Ala Gly Leu 1045 1050

Gly Leu Val Ala Ile Tyr Phe Ala Thr Gln Val Val Phe Asp Lys Ser 1060 1065 1070

Asp Leu Ala Lys Tyr Ser Ala 1075